AUGUST 2001
VOLUME 46
NUMBER 8
ISSN 0020-1324 RESP A_P

www.rcjournal.com

RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
46TH YEAR—ESTABLISHED 1956

47th International Respiratory Congress
Annual Convention & Exhibition
December 1-4, 2001, San Antonio, Texas

EDITORIALS

New International Guidelines for COPD

ORIGINAL CONTRIBUTIONS

A Prospective Randomized Trial of Protocol-Directed Versus Physician-Directed Weaning in Children

A Comparison of Two Airway Suctioning Frequencies in Mechanically Ventilated, Very-Low-Birthweight Infants

A Multivariate, Failure Time Analysis of 5 Common Ventilator Brands

SPECIAL ARTICLES

NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Executive Summary

Cause.

New for COPD!

And Effective.

Introducing premeasured, premixed DuoNeb.

It's the first and only one-step dual-therapy nebulizer solution for COPD, with improved efficacy over albuterol or ipratropium alone—and no increased safety risk.[1]

DuoNeb is indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator. In a 12-week clinical study, the most common adverse reactions reported with DuoNeb Inhalation Solution were chest pain, pharyngitis, diarrhea, bronchitis, nausea and leg cramps.

Albuterol sulfate can have a significant cardiovascular effect, significant hypokalemia and the potential life-threatening paradoxical bronchospasm. Caution is advised in patients with convulsive disorders, hyperthyroidism, diabetes mellitus, narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction. Co-administration of DuoNeb Inhalation Solution and other sympathomimetic agents may increase the risk of adverse cardiovascular effects.

Please see following page for prescribing information.

DuoNeb
(ipratropium bromide and albuterol sulfate)
Inhalation Solution
Nebulize 1 QID

The first and only one-step dual-therapy nebulizer solution for COPD.

Vial Contains: 0.5 mg Ipratropium Bromide
3.0 mg Albuterol Sulfate
(equivalent to **2.5 mg** Albuterol Base)

DEY 800-755-5560
www.deyinc.com

© 2001 DEY 09-773-00 4/01

Circle 150 on product info card

DuoNeb™

(Ipratropium Bromide 0.5 mg/Albuterol Sulfate 3.0 mg*)

Inhalation Solution

***Equivalent to 2.5 mg albuterol base**

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

DuoNeb is indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator

CONTRAINDICATIONS

DuoNeb is contraindicated in patients with a history of hypersensitivity to any of its components, or to atropine and its derivatives.

WARNINGS

Paradoxical Bronchospasm: In the clinical study of DuoNeb, paradoxical bronchospasm was not observed However, paradoxical bronchospasm has been observed with both inhaled ipratropium bromide and albuterol products and can be life-threatening. If this occurs, DuoNeb should be discontinued immediately and alternative therapy instituted

Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled products containing sympathomimetic amines and with the home use of nebulizers.

Cardiovascular Effect: DuoNeb, like other beta adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon for DuoNeb at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown Therefore, DuoNeb, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions to albuterol and/or ipratropium bromide may occur after the administration of DuoNeb as demonstrated by rare cases of urticaria, angioedema, rash, pruritus, oropharyngeal edema, bronchospasm, and anaphylaxis

PRECAUTIONS

General

1 Effects Seen with Sympathomimetic Drugs. As with all products containing sympathomimetic amines, DuoNeb should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis Additionally, β-agonists may cause a decrease in serum potassium in some patients, possibly through intracellular shunting The decrease is usually transient, not requiring supplementation

2 Effects Seen with Anticholinergic Drugs: Due to the presence of ipratropium bromide in DuoNeb, it should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder-neck obstruction

3 Use in Hepatic or Renal Diseases: DuoNeb has not been studied in patients with hepatic or renal insufficiency It should be used with caution in these patient populations.

Information for Patients

The action of DuoNeb should last up to 5 hours. DuoNeb should not be used more frequently than recommended. Patients should be instructed not to increase the dose or frequency of DuoNeb without consulting their healthcare provider. If symptoms worsen, patients should be instructed to seek medical consultation.

Patients must avoid exposing their eyes to this product as temporary papillary dilation, blurred vision, eye pain, or precipitation or worsening of narrow-angle glaucoma may occur, and therefore proper nebulizer technique should be assured, particularly if a mask is used

If a patient becomes pregnant or begins nursing while on DuoNeb, they should contact their healthcare provider about use of DuoNeb

See the illustrated Patient's Instruction for Use in the product package insert.

Drug Interactions

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is, therefore, advised in the co-administration of DuoNeb with other drugs having anticholinergic properties.

β-adrenergic agents: Caution is advised in the co-administration of DuoNeb and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects

β-receptor blocking agents: These agents and albuterol sulfate inhibit the effect of each other. β-receptor blocking agents should be used with caution in patients with hyperreactive airways, and if used, relatively selective ß, selective agents are recommended

Diuretics: The electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β-agonists, especially when the recommended dose of the β-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of β-agonist-containing drugs, such as DuoNeb, with non-potassium sparing diuretics.

Monoamine oxidase inhibitors or tricyclic antidepressants: DuoNeb should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents because the action of albuterol sulfate on the cardiovascular system may be potentiated

Carcinogenesis, Mutagenesis, Impairment of Fertility

Albuterol Sulfate. In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovanum at and above dietary doses of 2 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist

In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 140 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 20 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleous assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis)

Ipratropium bromide. In 2-year studies in Sprague-Dawley rats and CD-1 mice, ipratropium bromide showed no evidence of tumorigenicity at oral doses up to 6 mg/kg (approximately 15 times and 8 times the maximum recommended daily inhalation dose for adults in rats and mice respectively, on a mg/m^2 basis).

Ipratropium bromide was not mutagenic in the Ames test and mouse dominant lethal test. Ipratropium bromide was not clastogenic in a mouse micronucleous assay

A reproduction study in rats demonstrated decreased conception and increased resorptions when ipratropium bromide was administered orally at a dose of 90 mg/kg (approximately 240 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). These effects were not seen with a dose of 50 mg/kg (approximately 140 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy

TERATOGENIC EFFECTS Pregnancy Category C

Albuterol sulfate. *Pregnancy Category C* Albuterol sulfate has been shown to be teratogenic in mice A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate formation also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg isoproterenol (positive control)

A reproduction study in Stride rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established

Ipratropium bromide, *Pregnancy Category B* Reproduction studies in CD-1 mice, Sprague-Dawley rats and New Zealand rabbits demonstrated no evidence of teratogenicity at oral doses up to 10, 100, and 125 mg/kg, respectively (approximately 15, 270, and 680 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) Reproduction studies in rats and rabbits demonstrated no evidence of teratogenicity at inhalation doses up to 1.5 and 1.8 mg/kg, respectively (approximately 4 and 10 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). There are no adequate and well-controlled studies of the use of DuoNeb, albuterol sulfate, or ipratropium bromide in pregnant women. DuoNeb should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Labor and Delivery

Oral albuterol sulfate has been shown to delay preterm labor in some reports. Because of the potential of albuterol to interfere with uterine contractility, use of DuoNeb during labor should be restricted to those patients in whom the benefits clearly outweigh the risks

Nursing Mothers

It is not known whether the components of DuoNeb are excreted in human milk. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken as a nebulized solution. Because of the potential for tumorigenicity shown for albuterol sulfate in some animals, a decision should be made whether to discontinue nursing or discontinue DuoNeb, taking into account the importance of the drug to the mother

Pediatric Use

The safety and effectiveness of DuoNeb in patients below 18 years of age have not been established

Geriatric Use

Of the total number of subjects in clinical studies of DuoNeb, 62 percent were 65 and over, while 19 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out

ADVERSE REACTIONS

Adverse reaction information concerning DuoNeb was derived from the 12-week controlled clinical trial

ADVERSE EVENTS OCCURRING IN ≥ 1% OF ≥ 1 TREATMENT GROUP(S) AND WHERE THE COMBINATIDN TREATMENT SHOWED THE HIGHEST PERCENTAGE

Body System COSTART Term	Albuterol n (%)	Ipratropium n (%)	DuoNeb n (%)
NUMBER OF PATIENTS	761	754	765
N (%) Patients with AE	327 (43.0)	329 (43.6)	367 (48.0)
BODY AS A WHOLE			
Pain	8 (1.1)	4 (0.5)	10 (1.3)
Pain chest	11 (1.4)	14 (1.9)	20 (2.6)
DIGESTIVE			
Diarrhea	5 (0.7)	9 (1.2)	14 (1.8)
Dyspepsia	7 (0.9)	8 (1.1)	10 (1.3)
Nausea	7 (0.9)	6 (0.8)	11 (1.4)
MUSCULO-SKELETAL			
Cramps leg	8 (1.1)	6 (0.8)	11 (1.4)
RESPIRATORY			
Bronchitis	11 (1.4)	13 (1.7)	13 (1.7)
Lung Disease	36 (4.7)	34 (4.5)	49 (6.4)
Pharyngitis	27 (3.5)	27 (3.6)	34 (4.4)
Pneumonia	7 (0.9)	8 (1.1)	10 (1.3)
UROGENITAL			
Infection urinary tract	3 (0.4)	9 (1.2)	12 (1.6)

Additional adverse reactions reported in more than 1% of patients treated with DuoNeb included constipation and voice alterations

In the clinical trial, there was a 0.3% incidence of possible allergic-type reactions, including skin rash pruritus, and urticaria

Additional information derived from the published literature on the use of albuterol sulfate and ipratropium bromide singly or in combination includes precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, paradoxical bronchospasm, wheezing, exacerbation of COPD symptoms, drowsiness, aching, flushing, upper respiratory tract infection, palpitations, taste perversion, elevated heart rate, sinusitis, back pain and sore throat

DOSAGE AND ADMINISTRATION

The recommended dose of DuoNeb is one 3 mL vial administered 4 times per day via nebulization with up to 2 additional 3 mL doses allowed per day, if needed. Safety and efficacy of additional doses or increased frequency of administration of DuoNeb beyond these guidelines has not been studied and the safety and efficacy of extra doses of albuterol sulfate or ipratropium bromide in addition to the recommended doses of DuoNeb have not been studied.

The use of DuoNeb can be continued as medically indicated to control recurring bouts of bronchospasm. If a previously effective regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of worsening COPD, which would require reassessment of therapy.

A Pari-LC-Plus™ nebulizer (with face mask or mouthpiece) connected to a PRONE8™ compressor was used to deliver DuoNeb to each patient in one U.S. clinical study. The safety and efficacy of DuoNeb delivered by other nebulizers and compressors have not been established.

DuoNeb should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask

HOW SUPPLIED

DuoNeb is supplied as a 3-mL sterile solution for nebulization in sterile low-density polyethylene unit-dose vials Cards of five vials are placed into a foil pouch. Supplied in cartons as listed below

NDC 49502-672-30 30 vials per carton

NDC 49502-672-60 60 vials per carton

Store between 2°C and 25°C (36°F and 77°F). Protect from light

DEY Napa, CA 94558

03-485-21(8RS) May 2001

1 Gross N, Tashkin D, Miller R, et al Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease *Respiration*. 1998;65:354-362

AN INNOVATIVE TELEVISION SPECIAL

NEW ADVANCEMENTS IN ASTHMA:

CUTTING EDGE MEDICAL REPORT

ONE BREATH AT A TIME

Asthma is a serious, allergy-related breathing difficulty characterized by gasping, coughing, wheezing and sometimes a frightening inability to take a breath. Children suffer greatly with asthma, but many people are unaware that this disease affects adults as well. The number of asthma sufferers in the U.S. has increased to unprecedented numbers and has many physicians and researchers working hard to get at the cause. While we wrestle with air pollutants, some experts are faulting American's fetish with cleanliness.

Breakthroughs with treatments have made the fight for breath an easier one with understanding of particularly damaging allergens and hereditary backgrounds. If you or a family member suffer with Asthma, you need to watch this program to learn of the research that has produced new and better ways to treat it.

ASTHMA: One Breath At A Time is co-hosted by Sally Wenzel, M.D., Pulmonary Division, Department of Medicine, National Jewish Medical and Research Center in Denver and Robert Lemanske, M.D., Professor of Pediatrics and Medicine at the University of Wisconsin Hospital.

INFORMATION TELEVISION NETWORK
For information on air dates and times, or to order a VHS copy of the program, call **1-888-380-6500**
Visit us on the Internet at **www.itvisus.com**

WebMD

HEALTH NETWORK
www.TheHealthNetwork.com

This 30-minute documentary program is produced as part of ITV's award-winning series, *The Cutting Edge Medical Report* and airs over *The Fox Health Network*, and is made possible by an unrestricted educational grant from 3M Pharmaceuticals and The National Jewish Medical and Research Center in Denver, Colorado.

is what puts it ahead.

PURITAN BENNETT
840 Ventilator System

Modular Design • Dual Microprocessors
SmartAlert™ Alarms • *DualView*™ Touchscreen
BiLevel™ Feature • Tube Compensation

The *840*™ Ventilator system was designed for the future. We're in the hospitals, talking to customers and clinicians, observing treatments and trends. Invest in the *840* ventilator, and get a breath delivery platform that can be upgraded and enhanced as your clinical needs change.

PURITAN BENNETT
Ventilators

Stay ahead in ventilation technology.
Call your Puritan Bennett Sales Representative, or call 1.800.635.5267.

tyco
Healthcare

PURITAN
BENNETT

© [illegible] Puritan Bennett [illegible] All rights reserved.

Circle 145 on product info card

CONTENTS

AUGUST 2001 / VOLUME 46 / NUMBER 8

FOR INFORMATION, CONTACT:

AARC Membership or Other AARC Services
American Association for Respiratory Care
11030 Ables Ln
Dallas TX 75229-4593
(972) 243-2272 • Fax (972) 484-2720
http://www.aarc.org

Therapist Registration or Technician Certification
National Board for Respiratory Care
8310 Nieman Rd
Lenexa KS 66214
(913) 599-4200 • Fax (913) 541-0156
http://www.nbrc.org

Accreditation of Education Programs
Committee on Accreditation for Respiratory Care
1701 W Euless Blvd, Suite 300
Euless TX 76040
(817) 283-2835 • Fax (817) 354-8519
http://www.coarc.com

Grants, Scholarships, Community Projects
American Respiratory Care Foundation
11030 Ables Ln
Dallas TX 75229-4593
(972) 243-2272 • Fax (972) 484-2720

AARC Government Affairs Office
Director of Govt Affairs
Jill Eicher
1225 King St, Second Floor
Alexandria VA 22314
(703) 548-8538 Fax (703) 548-8499
eicher@aarc.org

Director of State Govt Affairs
Cheryl West MHA
8630 Braeswood Pt. #2
Colorado Springs, CO 80920
(719) 535-9970 west@aarc.org

RESPIRATORY CARE

RESPIRATORY CARE (ISSN 0020-1324, USPS 0489-190) is published monthly by Daedalus Enterprises Inc, at 11030 Ables Lane, Dallas TX 75229-4593, for the American Association for Respiratory Care. One volume is published per year beginning each January. Subscription rates are $75 per year in the US, $90 in all other countries (for airmail, add $94).

The contents of the Journal are indexed in *Index Medicus*/MEDLINE, Hospital and Health Administration Index, Cumulative Index to Nursing and Allied Health Literature, EMBASE/Exerpta Medica, and RNdex Library Edition. Abridged versions of RESPIRATORY CARE are also published in Italian, French, and Japanese, with permission from Daedalus Enterprises Inc.

Periodicals postage paid at Dallas TX and at additional mailing offices. POSTMASTER: Send address changes to RESPIRATORY CARE, Membership Office, Daedalus Enterprises Inc, 11030 Ables Lane, Dallas TX 75229-4593.

♾ Printed on acid-free paper
Printed in the United States of America
Copyright © 2001, by Daedalus Enterprises Inc

EDITORIALS

New International Guidelines for Chronic Obstructive Pulmonary Disease
by David J Pierson—Seattle, Washington **768**

ORIGINAL CONTRIBUTIONS

Weaning Children from Mechanical Ventilation: A Prospective Randomized Trial of Protocol-Directed Versus Physician-Directed Weaning
by Theresa Ryan Schultz, Richard J Lin, H Marc Watzman, Suzanne M Durning, Roberta Hales, Arnetta Woodson, Barbara Francis, Lisa Tyler, Linda Napoli, and Rodolfo I Godinez—Philadelphia, Pennsylvania **772**

A Comparison of Two Airway Suctioning Frequencies in Mechanically Ventilated, Very-Low-Birthweight Infants
by Leandro Cordero, Mercedes Sananes, and Leona W Ayers—Columbus, Ohio **783**

An Evaluation of Ventilator Reliability: A Multivariate, Failure Time Analysis of 5 Common Ventilator Brands
by Paul B Blanch—Gainesville, Florida **789**

SPECIAL ARTICLES

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): Executive Summary
by Romain A Pauwels—Ghent, Belgium; A Sonia Buist—Portland, Oregon; Peter MA Calverley—Liverpool, United Kingdom; Christine R Jenkins—Sydney, New South Wales, Australia; and Suzanne S Hurd—Bethesda, Maryland; on behalf of the GOLD Scientific Committee **798**

LETTERS

High-Frequency Jet Ventilation
by J Bert Bunnell—Salt Lake City, Utah
response by Dean R Hess—Boston, Massachusetts **826**

BOOKS, FILMS, TAPES, & SOFTWARE

Chronic Lung Disease in Early Infancy (Bland RD, Coalson JJ, editors)
reviewed by Keith J Barrington—Montreal, Quebec, Canada **829**

Voices and Choices: Young People Who Use Assisted Ventilation: Their Health and Social Care, and Education (Noyes J) *and* Voices and Choices: Young People Who Use Assisted Ventilation: Bibliography and Analysis of the Literature (Sudbery J and Noyes J)
reviewed by Redento D Ferranti—New Haven, Connecticut and John J Votto—Farmington, Connecticut **830**

Cystic Fibrosis: Medical Care (Orenstein DM, Rosenstein BJ, & Stern RC, editors)
reviewed by Demetrios S Theodoropoulos—Cleveland, Ohio **832**

Want to get out of the parts business?

GET THE GRAB 'N GO SYSTEM, PRAXAIR'S ALL-IN-ONE PORTABLE MEDICAL OXYGEN UNIT.

Praxair's *Grab 'n Go*™ portable medical oxygen system is an oxygen cylinder with a regulator and a contents gauge already attached. It's a fast, easy and safe way to dispense portable oxygen. With a *Grab 'n Go* oxygen unit, you're ready to go at a moment's notice.

Because the *Grab 'n Go* system has no separate parts, you don't waste time searching for and keeping track of equipment. You don't waste money maintaining and repairing equipment. And you don't hassle with wrenches and keys.

With Praxair's *Grab 'n Go* system you have everything you need. The built-in gauge lets you verify contents at a glance. And the easy-to-use regulator lets you adjust oxygen flow with the turn of a dial. The *Grab 'n Go* system also has a handle that makes it a cinch to carry.

Save time. End frustration. And get out of the parts business.

Want to try Praxair's *Grab 'n Go* oxygen system for free? Get up to 20 *Grab 'n Go* units to use in your facility for up to 3 months. To find out more about our demo program, call **1-800-299-7977 ext. 6961**, or visit **www.praxair.com/healthcare**. And while you're at it, check out our extensive line of respiratory gases, equipment and services.

PRAXAIR, the FLOWING AIRSTREAM design, GRAB 'N GO and GRAB 'N GO III are either trademarks or registered trademarks of Praxair Technology, Inc. in the United States and/or other countries.
2001 Praxair Technology, Inc. All rights reserved.
P-8564

PRAXAIR

Making our planet more productive

Visit AARC Booths 428,430 in San Antonio

Circle 122 on product info card

CONTENTS

CONTINUED

ALSO IN THIS ISSUE

839 AARC Membership Application

750 Abstracts from Other Journals

848 Advertisers Index & Help Lines

848 Author Index

846 Calendar of Events

841 Manuscript Preparation Guide

837 MedWatch

845 New Products

847 Notices

RESPIRATORY CARE

A Monthly Science Journal
Established in 1956

The Official Journal of the American Association for Respiratory Care

Pulmonary Rehabilitation: Guidelines to Success, 3rd edition (Hodgkin JE, Celli BR, Connors GL)
reviewed by Ronald G Beckett—Hamden, Connecticut 833

Advances in Cardiopulmonary Rehabilitation (Jobin J, Maltais F, LeBlanc P, Simard C, editors)
reviewed by Nicolino Ambrosino—Gussago, Italy 834

COMING IN NOVEMBER & DECEMBER:

Proceedings from the 28th RESPIRATORY CARE Journal Conference on

Evidence-Based Medicine in Respiratory Care

December 1-4, 2001
San Antonio, Texas

For 46 years the AARC's International Respiratory Congress has been the gold standard of respiratory care education and trade. For 46 years the AARC's International Respiratory Congress has delivered the highest quality programs with information that really matters. For 46 years the AARC has plowed its resources back into the profession, expanding the practice and influence of respiratory therapy in the health care system. Don't miss out on the largest and most comprehensive respiratory care meeting in the world, coming in 2001 to one of the most exciting cities in the US—San Antonio. For additional information, please call (972) 243-2272, or email clay@aarc.org.

AeroChamber Plus™ VHC

Performance Matters.

AARC ZENITH AWARD 1999

REGISTERED ISO 9001 QUALITY SYSTEM

The Gold Standard.

The Monaghan Medical tradition of innovation continues with the newly designed ***AeroChamber Plus***™ Valved Holding Chamber ("VHC"). Now, "The Gold Standard" has been set even higher.

Proven Performance.

The ***AeroChamber Plus***™ VHC consistently delivers a higher fine particle dose across a variety of metered dose inhalers ("MDIs"). For example, comparative *in vitro* testing with a competitive device revealed the ***AeroChamber Plus***™ VHC with Combivent® Inhalation Aerosol delivers up to 37% more albuterol, and up to 34% more ipratropium bromide per dose.[1]

Cost Effective.

With the ***AeroChamber Plus***™ VHC you have access to a higher fine particle delivery of more medicine from a single dose. In turn, the medicine may be more effective and fewer doses may be needed for therapeutic response. And with fewer doses needed, your patients can look forward to substantial savings.

Monaghan Medical's newly designed ***AeroChamber Plus***™ VHC with ***FLOWSIGnal***® Whistle – the new Gold Standard – is a proven performer, consistently delivering more medicine from a single dose.

monaghan™

Monaghan Medical Corporation
PO Box 2805 • Plattsburgh, NY 12901-0299
Customer Service 800-833-9653 • www.monaghanmed.com

™ trademark and ® registered trademarks
® Combivent is a trademark of
Boehringer Ingelheim Pharmaceuticals, Inc.
© 2000 Monaghan Medical Corporation.

1 Data on file

Circle 125 on product info card

EDITORIAL OFFICE

600 Ninth Avenue, Suite 702
Seattle WA 98104
(206) 223-0558
Fax (206) 223-0563
www.rcjournal.com

MANAGING EDITOR

Ray Masferrer RRT FAARC

ASSISTANT EDITOR

Katherine Kreilkamp

EDITORIAL ASSISTANT

Linda Barcus

COPY EDITOR

Matthew Mero

PRODUCTION

Kelly Piotrowski

MARKETING

Dale L Griffiths
Director of Marketing

Tim Goldsbury
Director, Advertising Sales

Beth Binkley
Advertising Assistant

PUBLISHER

Sam P Giordano MBA
RRT FAARC

RESPIRATORY CARE

A Monthly Science Journal
Established in 1956

The Official Journal of the
American Association for
Respiratory Care

EDITOR IN CHIEF

David J Pierson MD FAARC
Harborview Medical Center
University of Washington
Seattle, Washington

ASSOCIATE EDITORS

Richard D Branson RRT FAARC
University of Cincinnati
Cincinnati, Ohio

Dean R Hess PhD RRT FAARC
Massachusetts General Hospital
Harvard University
Boston, Massachusetts

James K Stoller MD
The Cleveland Clinic Foundation
Cleveland, Ohio

Charles G Durbin Jr MD FAARC
University of Virginia
Charlottesville, Virginia

Neil R MacIntyre MD FAARC
Duke University
Durham, North Carolina

EDITORIAL BOARD

Alexander B Adams MPH RRT FAARC
Regions Hospital
St Paul, Minnesota

Thomas A Barnes EdD RRT FAARC
Northeastern University
Boston, Massachusetts

Joshua O Benditt MD
University of Washington
Seattle, Washington

Michael J Bishop MD
University of Washington
Seattle, Washington

Lluis L Blanch MD PhD
Hospital de Sabadell
Sabadell, Spain

Bartolome R Celli MD
Tufts University
Boston, Massachusetts

Robert L Chatburn RRT FAARC
University Hospitals of Cleveland
Case Western Reserve University
Cleveland, Ohio

Patrick J Dunne MEd RRT FAARC
Health Care Productions
Fullerton, California

James B Fink MS RRT FAARC
Hines VA Hospital
Loyola University
Chicago, Illinois

John E Heffner MD
Medical University of South Carolina
Charleston, South Carolina

Mark J Heulitt MD FAARC
University of Arkansas
Little Rock, Arkansas

Leonard D Hudson MD
University of Washington
Seattle, Washington

Robert M Kacmarek PhD RRT FAARC
Massachusetts General Hospital
Harvard University
Boston, Massachusetts

Richard H Kallet MS RRT
San Francisco General Hospital
University of California San Francisco
San Francisco, California

Lucy Kester MBA RRT FAARC
The Cleveland Clinic Foundation
Cleveland, Ohio

Max Kirmse MD
University of Erlangen-Nurnberg
Erlangen, Germany

Toshihiko Koga MD
Koga Institute for Medical Research
Kuriume, Japan

Marin H Kollef MD
Washington University
St Louis, Missouri

Constantine A Manthous MD
Bridgeport Hospital
Bridgeport, Connecticut

John J Marini MD
University of Minnesota
St Paul, Minnesota

Shelley C Mishoe PhD RRT FAARC
Medical College of Georgia
Augusta, Georgia

Marcy F Petrini PhD
University of Mississippi
Jackson, Mississippi

Joseph L Rau PhD RRT FAARC
Georgia State University
Atlanta, Georgia

Catherine SH Sassoon MD
University of California Irvine
Long Beach, California

John W Shigeoka MD
Veterans Administration Medical Center
Salt Lake City, Utah

Martin J Tobin MD
Loyola University
Chicago, Illinois

Jeffrey J Ward MEd RRT
Mayo Medical School
Rochester, Minnesota

Robert L Wilkins PhD RRT FAARC
Loma Linda University
Loma Linda, California

STATISTICAL CONSULTANT

Gordon D Rubenfeld MD
University of Washington
Seattle, Washington

SECTION EDITORS

Hugh S Mathewson MD
Joseph L Rau PhD RRT FAARC
Drug Capsule

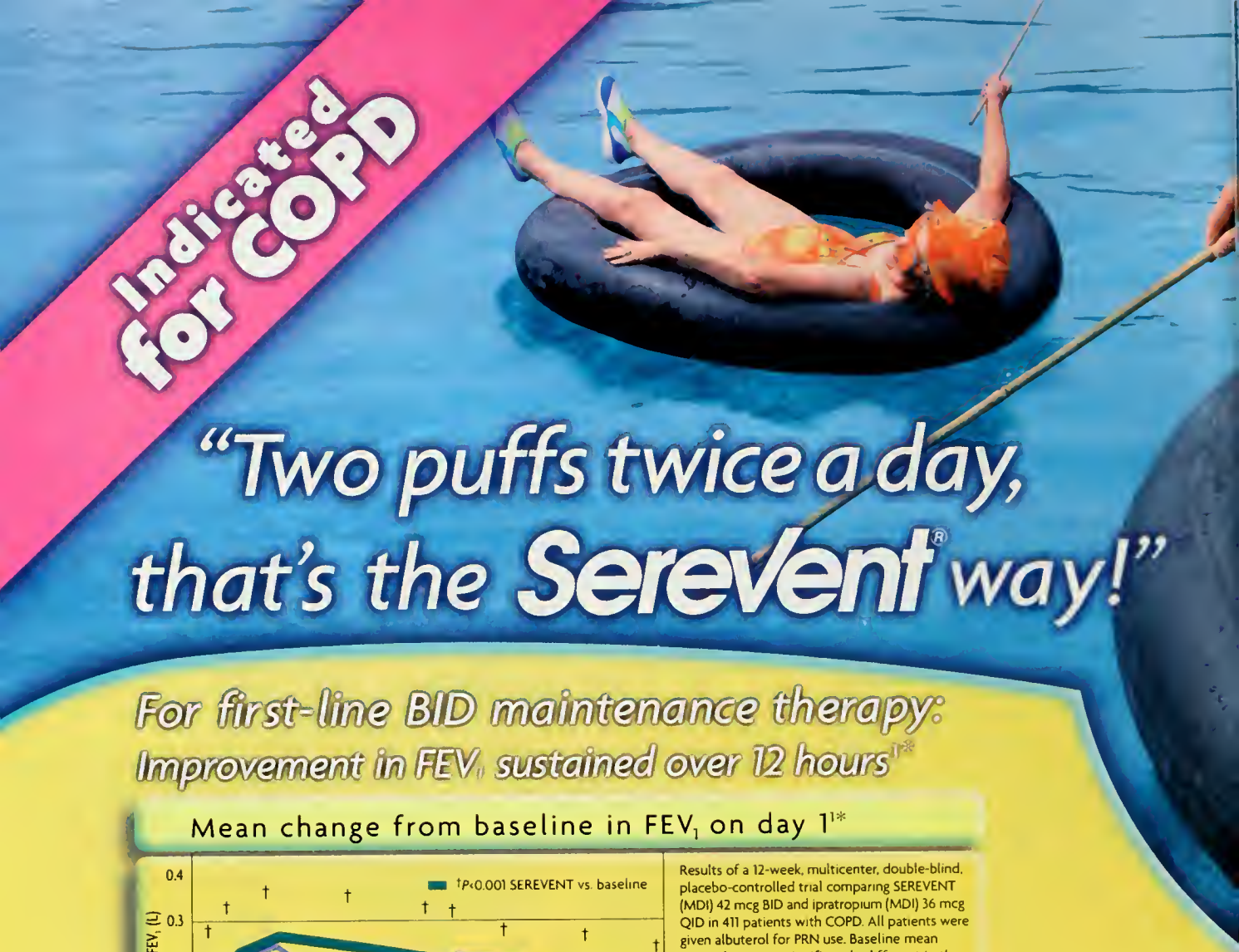
Richard D Branson RRT FAARC
Robert S Campbell RRT FAARC
Kuttredge's Corner

Steven B Nelson MS RRT
RC Web Sites

Jon Nilsestuen PhD RRT FAARC
Ken Hargett RRT
Graphics Corner

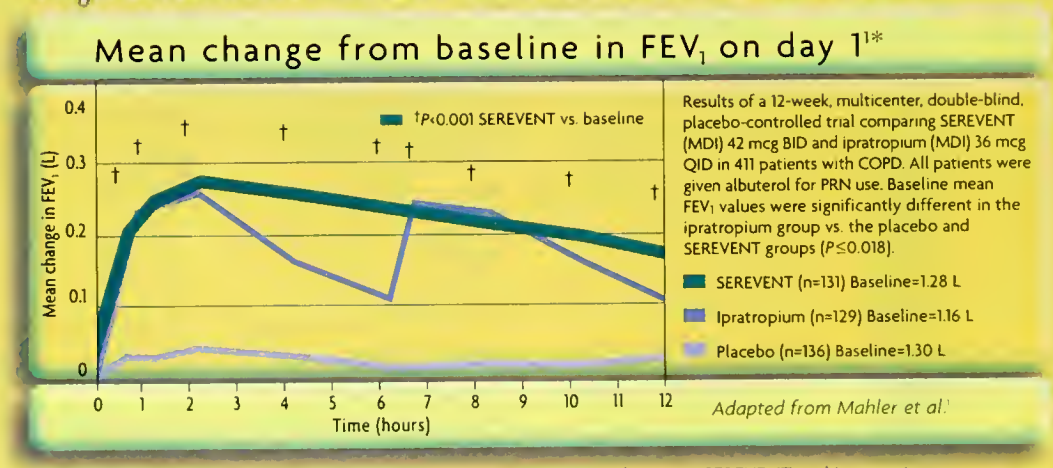
Charles G Irvin PhD
Gregg L Ruppel MEd RRT RPFT FAARC
PFT Corner

Patricia Ann Doorley MS RRT
Charles G Durbin Jr MD FAARC
Test Your Radiologic Skill



"Two puffs twice a day, that's the Serevent® way!"

For first-line BID maintenance therapy: Improvement in FEV_1 sustained over 12 hours[1]*


Mean change from baseline in FEV1 on day 1[1]*
†P<0.001 SEREVENT vs. baseline
Mean change in FEV1 (L)
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hours)
Results of a 12-week, multicenter, double-blind, placebo-controlled trial comparing SEREVENT (MDI) 42 mcg BID and ipratropium (MDI) 36 mcg QID in 411 patients with COPD. All patients were given albuterol for PRN use. Baseline mean FEV1 values were significantly different in the ipratropium group vs. the placebo and SEREVENT groups (P≤0.018).
SEREVENT (n=131) Baseline=1.28 L
Ipratropium (n=129) Baseline=1.16 L
Placebo (n=136) Baseline=1.30 L
Adapted from Mahler et al.[1]

*In clinical trials, no statistically significant difference in FEV_1 was seen between SEREVENT and ipratropium.

- *Daytime use of rescue albuterol reduced by 57% versus baseline at 12 weeks (baseline rescue albuterol 4.6 puffs/day)*[1]
- *Sustained efficacy over a 12-week period*[1]
- *In clinical trials, no consistently significant differences were seen among the treatment groups in the following parameters: 6-minute walk, quality-of-life symptom scores, dyspnea, incidence of exacerbations*

When beginning treatment with SEREVENT Inhalation Aerosol, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute COPD symptoms (see PRECAUTIONS: Information for Patients in complete Prescribing Information).

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO RELIEVE ACUTE COPD SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting, $beta_2$-agonist (e.g., albuterol) for treatment of acute COPD symptoms that occur despite regular twice-daily (morning and evening, approximately 12 hours apart) use of SEREVENT Inhalation Aerosol.

Please see brief summary of Prescribing Information and reference on following pages.

Circle 124 on product info card

For COPD

Serevent®

salmeterol xinafoate

Inhalation Aerosol

Choose 12-hour efficacy
Give BID convenience

GlaxoWellcome

SEREVENT®

BRIEF SUMMARY

(salmeterol xinafoate) Inhalation Aerosol

Bronchodilator Aerosol
For Oral Inhalation Only

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS: SEREVENT Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to salmeterol or any of its components.

WARNINGS:

IMPORTANT INFORMATION: SEREVENT INHALATION AEROSOL SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported, both in the United States and worldwide, when SEREVENT Inhalation Aerosol has been initiated in this situation.

Although it is not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT Inhalation Aerosol in this setting is inappropriate.

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting $beta_2$-agonist for this purpose as well as warn them that increasing inhaled $beta_2$-agonist use is a signal of deteriorating asthma.

SEREVENT INHALATION AEROSOL IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when SEREVENT Inhalation Aerosol is initiated.

(See PRECAUTIONS: Information for Patients and the accompanying PATIENT'S INSTRUCTIONS FOR USE.)

1. Do Not Introduce SEREVENT Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma. SEREVENT Inhalation Aerosol is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE section of full prescribing information) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that SEREVENT Inhalation Aerosol provides greater efficacy than or additional efficacy to inhaled, short-acting $beta_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported, both in the United States and worldwide, in patients receiving SEREVENT Inhalation Aerosol. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting $beta_2$-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits, sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

2. Do Not Use SEREVENT Inhalation Aerosol to Treat Acute Symptoms. An inhaled, short-acting $beta_2$-agonist, not SEREVENT Inhalation Aerosol, should be used to relieve acute asthma or COPD symptoms. When prescribing SEREVENT Inhalation Aerosol, the physician must also provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SEREVENT Inhalation Aerosol.

When beginning treatment with SEREVENT Inhalation Aerosol, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

3. Watch for Increasing Use of Inhaled, Short-Acting $Beta_2$-Agonists, Which Is a Marker of Deteriorating Asthma. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting $beta_2$-agonist becomes less effective or the patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting $beta_2$-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting $beta_2$-agonist is used in an 8-week period in conjunction with SEREVENT Inhalation Aerosol, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT Inhalation Aerosol in this situation is not appropriate. SEREVENT Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose of 2 inhalations.**

4. Do Not Use SEREVENT Inhalation Aerosol as a Substitute for Oral or Inhaled Corticosteroids: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids. There are no data demonstrating that SEREVENT Inhalation Aerosol has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating SEREVENT Inhalation Aerosol. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

5. Do Not Exceed Recommended Dosage: As with other inhaled $beta_2$-adrenergic drugs, SEREVENT Inhalation Aerosol should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT_c interval, which has the potential for producing ventricular arrhythmias.

6. Paradoxical Bronchospasm. SEREVENT Inhalation Aerosol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, SEREVENT Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

7. Immediate Hypersensitivity Reactions. Immediate hypersensitivity reactions may occur after administration of SEREVENT Inhalation Aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, and bronchospasm.

8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving SEREVENT Inhalation Aerosol.

SEREVENT Inhalation Aerosol, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of SEREVENT Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, SEREVENT Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

PRECAUTIONS:

General: 1. Use with Spacer or Other Devices. The safety and effectiveness of SEREVENT Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

2. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension, in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

3. Metabolic Effects. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. No effects on glucose have been seen with SEREVENT Inhalation Aerosol at recommended doses. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT Inhalation Aerosol at recommended doses.

Information for Patients: See illustrated PATIENT'S INSTRUCTIONS FOR USE. **SHAKE WELL BEFORE USING.**

It is important that patients understand how to use SEREVENT Inhalation Aerosol appropriately and how it should be used in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

1. Shake well before using.
2. The action of SEREVENT Inhalation Aerosol may last up to 12 hours or longer. The recommended dosage (2 inhalations twice daily, morning and evening) should not be exceeded.
3. SEREVENT Inhalation Aerosol is not meant to relieve acute asthma or COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).
4. Patients should not stop SEREVENT therapy for COPD without physician/provider guidance since symptoms may recur after discontinuation.
5. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma.
   - Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
   - Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
   - Use of 4 or more inhalations per day of a short-acting $beta_2$-agonist for 2 or more days consecutively
   - Use of more than one 200-inhalation canister of an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) in an 8-week period
6. SEREVENT Inhalation Aerosol should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT Inhalation Aerosol.
7. Patients should be cautioned regarding common adverse cardiovascular effects, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
8. In patients receiving SEREVENT Inhalation Aerosol, other inhaled medications should be used only as directed by the physician.
9. When using SEREVENT Inhalation Aerosol to prevent exercise-induced bronchospasm, patients should take the dose at least 30 to 60 minutes before exercise.
10. If you are pregnant or nursing, contact your physician about use of SEREVENT Inhalation Aerosol.
11. Effective and safe use of SEREVENT Inhalation Aerosol includes an understanding of the way that it should be administered.

Drug Interactions: ***Short-Acting Beta-Agonists:*** In the two 3-month, repetitive-dose clinical asthma trials (n=184), the mean daily need for additional $beta_2$-agonist use was 1 to 1½ inhalations per day, but some patients used more. Eight percent of patients used at least 8 inhalations per day at least on 1 occasion. Six percent used 9 to 12 inhalations at least once. There were 15 patients (8%) who averaged over 4 inhalations per day. Four of these used an average of 8 to 11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than 8 inhalations per day of short-acting $beta_2$-agonists with SEREVENT Inhalation Aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving SEREVENT Inhalation Aerosol, nebulized albuterol (1 dose in most) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of SEREVENT Inhalation Aerosol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving SEREVENT Inhalation Aerosol has not been completely evaluated. In 1 clinical asthma trial, 87 patients receiving SEREVENT Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by SEREVENT Inhalation Aerosol therapy.

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as SEREVENT Inhalation Aerosol, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate at oral doses of 1.4 mg/kg and above (approximately 9 times the maximum recommended daily inhalation dose in adults based on comparison of the areas under the plasma concentration versus time curves [AUCs]) caused dose-related increases in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (comparable to the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

In a 24-month inhalation and oral carcinogenicity study in Sprague Dawley rats, salmeterol caused dose-related increases in the incidence of mesovarian leiomyomas and ovarian cysts at inhalation and oral doses of 0.68 mg/kg per day and above (approximately 55 times the maximum recommended human daily inhalation dose in adults on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg per day (approximately 15 times the maximum recommended human daily inhalation dose in adults on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg (approximately 160 times the maximum recommended human daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. No teratogenic effects occurred in the rat at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended human daily inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation dose in adults based on the comparison of the AUCs), salmeterol xinafoate exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation: these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at oral doses of 10 mg/kg (approximately 1600 times the maximum recommended human daily inhalation dose on a mg/m² basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with SEREVENT Inhalation Aerosol in pregnant women. SEREVENT Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SEREVENT Inhalation Aerosol for prevention of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in milk. However, since there is no experience with use of SEREVENT Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SEREVENT Inhalation Aerosol in children younger than 12 years of age have not been established.

Geriatric Use: Of the total number of patients who received SEREVENT Inhalation Aerosol in all asthma clinical studies, 241 were 65 years of age and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in 4 well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in 2 large parallel-group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the 2 latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

In 2 large, randomized, double-blind, placebo-controlled 3-month studies involving patients with COPD, 133 patients using SEREVENT Inhalation Aerosol were 65 years and older. These patients experienced similar improvements in FEV_1 as observed for patients younger than 65.

No apparent differences in the efficacy and safety of SEREVENT Inhalation Aerosol were observed when geriatric patients were compared with younger patients in asthma and COPD clinical trials. As with other beta$_2$-agonists, however, special caution should be observed when using SEREVENT Inhalation Aerosol in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

ADVERSE REACTIONS: Adverse reactions to salmeterol are similar in nature to reactions to other selective beta$_2$-adrenoceptor agonists, i.e., tachycardia, palpitations, immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS), headache, tremor, nervousness, and paradoxical bronchospasm (see WARNINGS).

Asthma: Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT Inhalation Aerosol in patients 12 years of age and older with asthma. Table 1 reports the incidence of adverse events in these 2 studies.

Table 1: Adverse Experience Incidence in 2 Large 12-Week Asthma Clinical Trials*

	Percent of Patients		
Adverse Event Type	Placebo n=187	SEREVENT Inhalation Aerosol 42 mcg twice daily n=184	Albuterol Inhalation Aerosol 180 mcg 4 times daily n=185
Ear, nose, and throat			
Upper respiratory tract infection	13	14	16*
Nasopharyngitis	12	14	11
Disease of nasal cavity/sinus	4	6	1
Sinus headache	2	4	<1
Gastrointestinal			
Stomachache	0	4	0
Neurological			
Headache	23	28	27
Tremor	2	4	3
Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

*The only adverse experience classified as serious was 1 case of upper respiratory tract infection in a patient treated with albuterol.

Table 1 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the SEREVENT Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Cardiovascular: Tachycardia, palpitations.

Ear, Nose, and Throat: Rhinitis, laryngitis.

Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.

Hypersensitivity: Urticaria.

Mouth and Teeth: Dental pain.

Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.

Neurological: Nervousness, malaise/fatigue.

Respiratory: Tracheitis/bronchitis.

Skin: Rash/skin eruption.

Urogenital: Dysmenorrhea.

Data from small dose-response studies show an apparent dose relationship for tremor, nervousness, and palpitations.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol or might otherwise be expected with the use of inhaled corticosteroids.

COPD: Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT Inhalation Aerosol in patients with COPD. Table 2 reports the incidence of adverse events in these 2 studies.

Table 2: Adverse Experience Incidence in 2 Large 12-Week COPD Clinical Trials

	Percent of Patients		
Adverse Event Type	Placebo n=278	SEREVENT Inhalation Aerosol 42 mcg twice daily n=267	Ipratropium Inhalation Aerosol 36 mcg 4 times daily n=271
Ear, nose, and throat			
Upper respiratory tract infection	7	9	9
Sore throat	3	8	6
Nasal sinus infection	1	4	2
Gastrointestinal			
Diarrhea	3	5	4
Musculoskeletal			
Back pain	3	4	3
Neurological			
Headache	10	12	8
Respiratory			
Chest congestion	3	4	3

Table 2 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

Common cold, rhinorrhea, bronchitis, cough, exacerbation of chest congestion, chest pain, and dizziness occurred at 3% or more but were equally common on placebo. Other events occurring in the SEREVENT Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Ear, Nose, and Throat: Cold symptoms, earache, epistaxis, nasal congestion, nasal sinus congestion, sneezing.

Gastrointestinal: Nausea, dyspepsia, gastric pain, gastric upset, abdominal pain, constipation, heartburn, oral candidiasis, xerostomia, vomiting, surgical removal of tooth.

Musculoskeletal: Leg cramps, myalgia, neck pain, pain in arm, shoulder pain, muscle injury of neck.

Neurological: Insomnia, sinus headache.

Non-Site Specific: Fatigue, fever, pain in body, discomfort in chest.

Respiratory: Acute bronchitis, dyspnea, influenza, lower respiratory tract infection, pneumonia, respiratory tract infection, shortness of breath, wheezing.

Urogenital: Urinary tract infection.

Electrocardiographic Monitoring in Patients With COPD: Continuous electrocardiographic (Holter) monitoring was performed on 284 patients in 2 large COPD clinical trials during five 24-hour periods. No cases of sustained ventricular tachycardia were observed. At baseline, non-sustained, asymptomatic ventricular tachycardia was recorded for 7 (7.1%), 8 (9.4%), and 3 (3.0%) patients in the placebo, SEREVENT, and ipratropium groups, respectively. During treatment, nonsustained, asymptomatic ventricular tachycardia that represented a clinically significant change from baseline was reported for 11 (11.6%), 15 (18.3%), and 20 (20.8%) patients receiving placebo, SEREVENT, and ipratropium, respectively. Four of these cases of ventricular tachycardia were reported as adverse events (1 placebo, 3 SEREVENT) by 1 investigator based upon review of Holter data. One case of ventricular tachycardia was observed during ECG evaluation of chest pain (ipratropium) and reported as an adverse event.

Observed During Clinical Practice: In extensive US and worldwide postmarketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS no. 1), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

The following events have also been identified during postapproval use of SEREVENT in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to SEREVENT.

Respiratory: Rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Cardiovascular: Hypertension, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles).

OVERDOSAGE: The expected signs and symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QT interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of SEREVENT Inhalation Aerosol.

Treatment consists of discontinuation of SEREVENT Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of SEREVENT Inhalation Aerosol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in rats at inhalation doses of 2.9 mg/kg (approximately 240 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in dogs at 0.7 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6100 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in rats at 1000 mg/kg (approximately 81,000 times the maximum recommended human daily inhalation dose on a mg/m² basis).

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent Nos. 4,992,474, 5,225,445, and 5,380,922

© Copyright 1994, 1998, 2000, Glaxo Wellcome Inc. All rights reserved.
July 2000 RL-851

Reference: 1. Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest.* 1999;115:957-965.

© 2000, Glaxo Wellcome Inc. All rights reserved.

Printed in USA SE2192R0 July 2001

Editorials, Commentaries, and Reviews To Note

Evidence Base for Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease—Snow V, Lascher S, Mottur-Pilson C. Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians-American Society of Internal Medicine. Ann Intern Med 2001;134(7):595-599.

Principles of Appropriate Antibiotic Use for Treatment of Acute Bronchitis in Adults—Snow V, Mottur-Pilson C, Gonzales R, for the American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine; Centers for Disease Control; Infectious Diseases Society of America. Ann Intern Med 2001;134(6):518-520.

Principles of Appropriate Antibiotic Use for Acute Sinusitis in Adults—Snow V, Mottur-Pilson C, Hickner JM, for the American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine; Centers for Disease Control; Infectious Diseases Society of America. Ann Intern Med 2001;134(6):495-497.

Principles of Appropriate Antibiotic Use for Treatment of Nonspecific Upper Respiratory Tract Infections in Adults—Snow V, Mottur-Pilson C, Gonzales R, for the American College of Physicians-American Society of Internal Medicine; American Academy of Family Physicians; Centers for Disease Control; Infectious Diseases Society of America. Ann Intern Med 2001; 134(6):487-489.

What's New about Ventilator-Associated Pneumonia—Kollef MH. Anesthesiology 2001; 94(3):551-553.

Dyspnea Near The End Of Life: An Excerpt from the Upcoming RNS 11th Annual Conference—Matzo ML, Balkstra CR, Zugcic M. Heart Lung 2001;30(2):164-165.

Moving from Compliance to Conscience: Why We Can and Should Improve on the Ethics of Clinical Research (commentary)—Kahn JP, Mastroianni AC. Arch Intern Med 2001;161(7): 925-928.

Model for Directly Assessing and Improving Clinical Competence and Performance in Revalidation of Clinicians—McKinley RK, Fraser RC, Baker R. BMJ 2001;322(7288):712-715.

The Diagnosis of Brain Death—Wijdicks EF. N Engl J Med 2001;344(16):1215-1221.

Which Guidelines Can We Trust? Assessing Strength of Evidence Behind Recommendations for Clinical Practice—Liberati A, Buzzetti R, Grilli R, Magrini N, Minozzi S. West J Med 2001;174(4):262-265.

Helping Pregnant Smokers Quit: Meeting the Challenge in the Next Decade—Orleans CT, Johnson RW, Barker DC, Kaufman NJ, Marx JF. West J Med 2001;174(4):276-281.

Collaborative Quality Improvement for Neonatal Intensive Care. NIC/Q Project Investigators of the Vermont Oxford Network—Horbar JD, Rogowski J, Plsek PE, Delmore P, Edwards WH, Hocker J, et al. Pediatrics 2001 Jan;107(1):14–22.

OBJECTIVE: To make measurable improvements in the quality and cost of neonatal intensive care using a multidisciplinary collaborative quality improvement model. DESIGN: Interventional study. Patient demographic and clinical information for infants with birth weight 501 to 1500 g was collected using the Vermont Oxford Network Database for January 1, 1994 to December 31, 1997. SETTING: Ten self-selected neonatal intensive care units (NICUs) received the intervention. They formed 2 subgroups (6 NICUs working on infection, 4 NICUs working on chronic lung disease). Sixty-six other NICUs served as a contemporaneous comparison group. PATIENTS: Infants with birth weight 501 to 1500 g born at or admitted within 28 days of birth between 1994 and 1997 to the 6 study NICUs in the infection group (n = 3063) and the 66 comparison NICUs (n = 21 509); infants with birth weight 501 to 1000 g at the 4

Meet Regulatory CE Requirements the Easy Way!

Professor's Rounds

Respiratory Care CE Credits: Each program approved for 1 hour of continuing education credit by Continuing Respiratory Care Education (CRCE)

Nursing CE Credit: Each program is approved for 1.2 hours of continuing education credit by the Texas Nurse Association

program 1

Taking the Mystery Out of Weaning the Pediatric Patient from the Ventilator

Peter Betit, BS, RRT, FAARC, and Richard D. Branson, BA, RRT, FAARC

Learn when to begin the process, how to recognize critical events in weaning a pediatric patient, and why weaning of the pediatric patient is different

Videotape available

program 2

Pulmonary Rehabilitation: Standard Care for Chronic Lung Disease Patients

Trina Limberg, BS, RRT, and Thomas J. Kallstrom, RRT, FAARC

Presentation details when to refer a patient for pulmonary rehabilitation; how to successfully operate a rehabilitation service, and how to prepare a treatment plan during assessment.

Videotape available

program 3

Noninvasive Ventilation: The Latest Word

Dean R. Hess, PhD, RRT, FAARC, and Richard D.Branson, BA, RRT, FAARC

Learn how to avoid intubation through identification of patients most likely to benefit from noninvasive ventilation. Learn selection and proper fit of full masks or nasal masks and how to select the proper ventilator.

Videotape available

program 4

Education of the Patient with Asthma

Tracey Mitchell, RRT, RPFT, and Thomas J. Kallstrom, RRT, FAARC

This program teaches how to ensure that patients understand the disease and their care plan for effective disease management. And, it details what patient education materials are available.

Sponsored in part by an educational grant from Sepracor, Inc.

Videotape available

program 5

ARDS: The Disease and Its Management

Leonard D. Hudson, MD, and David J. Pierson, MD, FAARC

Presents ARDS diagnostic criteria and clinical risk factors. Teaches viewers the implications of the lower and upper inflection points on the pressure-volume curve; and the calculation of estimated required tidal volume.

Live Videoconference -
June 26, 11:30 a.m. - 1:00 p.m. CDT
Teleconference with Videotape
July 17, 11:30 a.m. - 12:00 Noon CDT

program 6

New Respiratory Drugs: What, When, and How?

Joseph L. Rau, PhD, RRT, FAARC, and Patrick J. Dunne, MEd, RRT, FAARC

Learn racemic drug mixtures and single isomers and their effective duration and how they lower costs and improve patient responses. Viewers learn the use of improved anticholinergics and inhaled anti-infective agents.

Sponsored in part by an educational grant from Sepracor, Inc.

Live Videoconference
Aug.14, 11:30 a.m. - 1:00 p.m. CDT
Teleconference with Videotape -
Sept.11, 11:30 a.m. - 12:00 Noon CDT

program 7

Invasive Ventilation: The Latest Word

Richard Kallet, MS, RRT, and Richard D. Branson, BA, RRT, FAARC

Learn how to avoid harming the patient and understand the function and also learn how reducing the work of breathing reduces the additional load on ventilatory musculature, and about reinflating lungs and enhancing the functional area of the lung

Live Videoconference
Sept. 25, 11:30 a.m. - 1:00 p.m. CDT
Teleconference with Videotape
Oct. 16, 11:30 a.m. - 12:00 Noon CDT

program 8

Test Your Lungs, Know Your Numbers, Prevent Emphysema

Thomas L. Petty, MD, FAARC, and David J. Pierson, MD, FAARC

Reviews the signs of COPD with emphasis on emphysema and on the measures used to relieve symptoms and slow the disease progression. Covers the importance of pulmonary function tests.

Sponsored in part by an educational grant from Boehringer Ingelheim, Inc.

Live Videoconference -
Oct. 23, 11:30 a.m. - 1:00 p.m. CDT
Teleconference with Videotape -
Nov. 20, 11:30 a.m. - 12:00 Noon CDT

REGISTRATION 2001

☐ **SINGLE PROGRAMS**
$245 Per Facility ($215 for AARC Members)

☐ Payment Enclosed Charge to: ☐ Visa ☐ Mastercard
☐ Purchase Order (P.O.)

Credit Card or P.O. No _____

Exp. Date _____

Signature (Required for Credit Card and P.O.) _____

Amount of Order $ _____ AARC Member No. _____
(Required for Discount)

SHIP PROGRAM MATERIALS TO (NO POST OFFICE BOXES):

Name _____
Department _____
Facility _____
Address _____
City/State/Zip _____
Telephone _____ E-mail Address _____

BILL TO (IF DIFFERENT FROM SHIPPING ADDRESS):

Name _____
Department _____
Facility _____
Address _____
City/State/Zip _____
Telephone _____

RECEPTION OPTIONS

(You Must Select One Only)

☐ Live Television Videoconference (C-Band)
☐ Teleconference with Videotape and Telephone Q&A
☐ Videotape Only (No CE Credit)*

*Videotapes will not be available until after the live videoconference and do not include course materials

CHECK THE DESIRED PROGRAMS

☐ Entire Series of Eight
☐ #1 Videotape only
☐ #2 Videotape only
☐ #3 Videotape only
☐ #4 Videotape only
☐ #5
☐ #6
☐ #7
☐ #8

PROFESSOR'S ROUNDS 2001
Telephone (972) 243-2272
Facsimile (972) 484-2720
11030 Ables Lane • Dallas, Texas 75229-4593

study NICUs in the chronic lung disease group (n = 738). INTERVENTIONS: NICUs formed multidisciplinary teams that worked together under the direction of a trained facilitator over a 3-year period beginning in January 1995. They received instruction in quality improvement, reviewed performance data, identified common improvement goals, and implemented "potentially better practices" developed through analysis of the processes of care, literature review, and site visits. MAIN OUTCOME MEASURES: The rates of infection after the third day of life with coagulase-negative staphylococcal or other bacterial pathogens for infants with birth weight 501 to 1500 g, and the rates of oxygen supplementation or death at 36 weeks' adjusted gestational age for infants with birth weight 501 to 1000 g. RESULTS: Between 1994 and 1996, the rate of infection with coagulase-negative staphylococcus decreased from 22.0% to 16.6% at the 6 project NICUs in the infection group; the rate of supplemental oxygen at 36 weeks' adjusted gestational age decreased from 43.5% to 31.5% at the 4 NICUs in the chronic lung disease group. There was heterogeneity in the effects among the NICUs in both project groups. The changes observed at the project NICUs for these outcomes were significantly larger than those observed at the 66 comparison NICUs over the 4-year period from 1994 to 1997. CONCLUSION: We conclude that multidisciplinary collaborative quality improvement has the potential to improve the outcomes of neonatal intensive care.

Economic Implications of Neonatal Intensive Care Unit Collaborative Quality Improvement—Rogowski JA, Horbar JD, Plsek PE, Baker LS, Deterding J, Edwards WH, et al. Pediatrics 2001 Jan;107(1):23–29.

OBJECTIVE: To make measurable improvements in the quality and cost of neonatal intensive care using a multidisciplinary collaborative quality improvement model. DESIGN: Interventional study. Data on treatment costs were collected for infants with birth weight 501 to 1500 g for the period of January 1, 1994 to December 31, 1997. Data on resources expended by hospitals to conduct this project were collected in a survey for the period January 1, 1995 to December 31, 1996. SETTING: Ten self-selected neonatal intensive care units (NICUs) received the intervention. They formed 2 subgroups (6 NICUs working on infection, 4 NICUs working on chronic lung disease). Nine other NICUs served as a contemporaneous comparison group. PATIENTS: Infants with birth weight 501 to 1500 g born at or admitted within 28 days of birth between 1994 and 1997 to the 6 study NICUs in the infection group (N = 2993) and the 9 comparison NICUs (N = 2203); infants with birth weight 501 to 1000 g at the 4 study NICUs in the chronic lung disease group (N = 663) and the 9 comparison NICUs (N = 1007). INTERVENTIONS: NICUs formed multidisciplinary teams which worked together to undertake a collaborative quality improvement effort between January 1995 and December 1996. They received instruction in quality improvement, reviewed performance data, identified common improvement goals, and implemented "potentially better practices" developed through analysis of the processes of care, literature review, and site visits. MAIN OUTCOME MEASURES: Treatment cost per infant is the primary economic outcome measure. In addition, the resources spent by hospitals in undertaking the collaborative quality improvement effort were determined. RESULTS: Between 1994 and 1996, the median treatment cost per infant with birth weight 501 to 1500 g at the 6 project NICUs in the infection group decreased from $57 606 to $46 674 (a statistical decline); at the 4 chronic lung disease hospitals, for infants with birth weights 501 to 1000 g, it decreased from $85 959 to $77 250. Treatment costs at hospitals in the control group rose over the same period. There was heterogeneity in the effects among the NICUs in both project groups. Cost savings were maintained in the year following the intervention. On average, hospitals spent $68 206 in resources to undertake the collaborative quality improvement effort between 1995 and 1996. Two thirds of these costs were incurred in the first year, with the remaining third in the second year. The average savings per hospital in patient care costs for very low birth weight infants in the infection group was $2.3 million in the post-intervention year (1996). There was considerable heterogeneity in the cost savings across hospitals associated with participation in the collaborative quality improvement project. CONCLUSION: Cost savings may be achieved as a result of collaborative quality improvement efforts and when they occur, they appear to be sustainable, at least in the short run. In high-cost patient populations, such as infants with very low birth weights, cost savings can quickly offset institutional expenditures for quality improvement efforts.

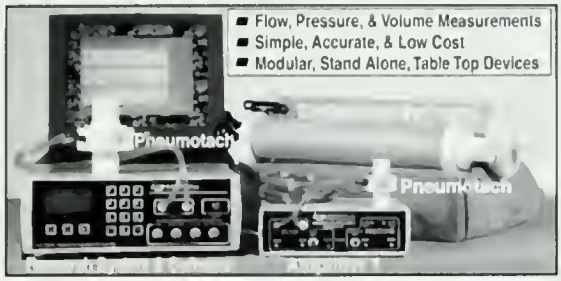
Expiratory Time Constants in Mechanically Ventilated Patients with and without COPD—Lourens MS, van den Berg B, Aerts JG, Verbraak AF, Hoogsteden HC, Bogaard JM. Intensive Care Med 2000 Nov;26(11): 1612–1618.

OBJECTIVE: In mechanically ventilated patients, the expiratory time constant provides information about the respiratory mechanics and the actual time needed for complete expiration. As an easy method to determine the time constant, the ratio of exhaled tidal volume to peak expiratory flow has been proposed. This assumes a single compartment model for the whole expiration. Since the latter has to be questioned in patients with chronic obstructive pulmonary disease (COPD), we compared time constants calculated from various parts of expiration and related these to time constants assessed with the interrupter method. DESIGN: Prospective study. SETTING: A medical intensive care unit in a university hospital. PATIENTS: Thirty-eight patients (18 severe COPD, eight mild COPD, 12 other pathologies) were studied during mechanical ventilation under sedation and paralysis. MEASUREMENTS AND RESULTS: Time constants determined from flow-volume curves at 100%, the last 75, 50, and 25% of expired tidal volume, were compared to time constants obtained from interrupter measurements. Furthermore, the time constants were related to the actual time needed for complete expiration and to the patient's pulmonary condition. The time constant determined from the last 75% of the expiratory flow-volume curve (RCfv75) was in closest agreement with the time constant obtained from the interrupter measurement, gave an accurate estimation of the actual time needed for complete expiration, and was discriminative for the severity of COPD. CONCLUSIONS: In mechanically ventilated patients with and without COPD, a time constant can well be calculated from the expiratory flow-volume curve for the last 75% of tidal volume, gives a good estimation of respiratory mechanics, and is easy to obtain at the bedside.

Acute Respiratory Distress Syndrome in Trauma Patients: ICU Mortality and Prediction Factors—Navarrete-Navarro P, Ruiz-Bailen M, Rivera-Fernandez R, Guerrero-Lopez F, Pola-Gallego-de-Guzman MD, Vazquez-Mata G. Intensive Care Med 2000 Nov;26(11):1624–1629.

OBJECTIVES: To study the factors that influence the intensive care unit (ICU) mortality of trauma patients who develop acute respiratory distress syndrome (ARDS) and to evaluate determinants of length of ICU stay among these patients. DESIGN: Study on a prospective cohort of 59 trauma patients that developed ARDS. SETTING: ICU of a referral trauma center. Fifty-nine patients were included during the study period from 1994 to 1997. METHODS: The dependent variables studied were the mortality and length of ICU stay. The main independent variables studied included the general severity score APACHE III, the revised trauma and injury severity scores (RTS, ISS), emergency treatment measures, the gas exchange index (P_{aO_2}/F_{IO_2}) recorded after the onset of ARDS and the development of multiple system organ failure (MSOF). Univariate and multivariate analyses were performed. RESULTS: The mean age of patients was 42.1 ± 16.7 years, 49 patients (83 %) were male, the mean APACHE III score was 52.7 ± 33.7 points, the ISS 28.5 ± 11.4 points and the RTS 8.9 ± 2.5 points. ICU length of stay was 28.5 ± 24.5 days and the mortality rate 31.7 % (19 deaths). Mortality was associated with the following: P_{aO_2}/F_{IO_2} ratio on the 3rd, 5th and 7th days post-ARDS; high volume of crystalloid/colloid infusion during resusci-

NEW! Hans Rudolph NEW!
Introduces Families of
INSTRUMENTATION MODULES,
PNEUMOTACHS & CALIBRATION SYRINGES



Research Pneumotach Systems with Windows™ Software
- RSS 100HR Model for use with Rudolph Linear Screen Pneumotachs
- RSS 100 Model for use with Fixed-Orifice Pneumotachs.
- Windows™ Software for displaying, storing, and reviewing data.
- Corrects for gas density, viscosity, temperature, and pressure.
- View LCD on module or connect serial RS232 to computer.

Pneumotach Amplifier 1
- Analog Outputs for flow and pressure.
- Analog Outputs configured for different voltage requirements.
- Offset and gain adjustment pots.

Linear and Bi-Directional Screen Pneumotachs
- Heated and Non-Heated Models.
- 8 calibrated flow ranges: 0-3, 0-5, 0-10, 0-35, 0-100, 0-160, 0-400, and 0-800 L/min.

Volume Calibration Syringes
- 6 calibrated volume sizes available: 7, 3, 1 & 1/2 Liter, 100ml and 10ml.

HANS RUDOLPH, inc. CE ISO 9001 EN 46001
MAKERS OF RESPIRATORY VALVES SINCE 1938
TEL: (816) 363-5522 USA & CANADA (800) 456-6695
FAX: (816) 822-1414 E-Mail: hri@rudolphkc.com www.rudolphkc.com
7205 CENTRAL, KANSAS CITY, MISSOURI 64114 U.S.A

Circle 127 on product info card

KAISER PERMANENTE

Great People. Great Medicine.
Great Opportunities.

Health care is changing. Kaiser Permanente leads the way. More than eight million people rely on us for their health care. Join our outstanding team and make a difference — every day.

We have great opportunities and offer excellent benefit packages for our team members and dependents, plus employment incentives that enhance your career and support you personally and professionally.

- Exceptional Salaries • Tuition Reimbursement
- Comprehensive Health Care
- And much more. . .

Respiratory Care Practitioner
(Full-Time, Part-Time and On Call)

For opportunities in California please call
(800) 331-3976
Visit our employment Web site at
www.kp.org/jobs
Please reference Source Code RC0801 when responding to this ad.

KAISER PERMANENTE®
California
EEO/AA/M/F/D/V Employer
Principals Only/No Search-Recruitment Agencies

Circle 121 on product info card

tation; the APACHE III score; and the development of MSOF. According to the multivariate analysis, the mortality of these patients was correlated with the P_{aO_2}/F_{IO_2} ratio on the 3rd day of ARDS, the APACHE III score and the development of MSOF. This analysis also showed days on mechanical ventilation to be the only variable that predicted ICU length of stay. CONCLUSIONS: The ICU mortality of trauma patients with ARDS is related to the APACHE III score, the gas exchange evolution as measured by the P_{aO_2}/F_{IO_2} on the 3rd day and the progressive complications indicated by the onset of MSOF. The length of ICU stay of these patients is related to the number of days on mechanical ventilation.

High Survival in Adult Patients with Acute Respiratory Distress Syndrome Treated by Extracorporeal Membrane Oxygenation, Minimal Sedation, and Pressure Supported Ventilation—Linden V, Palmer K, Reinhard J, Westman R, Ehren H, Granholm T, Frenckner B. Intensive Care Med 2000 Nov;26(11):1630–1637.

OBJECTIVES: To evaluate the results of treatment of severe acute respiratory distress syndrome (ARDS) with extracorporeal membrane oxygenation (ECMO), minimal sedation, and pressure supported ventilation. DESIGN AND SETTING: Observational study in a tertiary referral center, Intensive Care Unit, Astrid Lindgren Children's Hospital at Karolinska Hospital, Stockholm, Sweden. SUBJECTS AND METHODS: Seventeen adult patients with ARDS were treated with venovenous or venoarterial ECMO after failure of conventional therapy. The Murray score of pulmonary injury averaged 3.5 (3.0–4.0) and the mean P_{aO_2}/F_{IO_2} ratio was 46 (31–65). A standard ECMO circuit with nonheparinized surfaces was used. The patients were minimally sedated and received pressure-supported ventilation. High inspiratory pressures were avoided and arterial saturation as low as 70% was accepted on venovenous bypass. RESULTS: In one patient a stable bypass could not be established. Among the remaining 16 patients 13 survived (total survival rate 76%) after 3–52 days (mean 15) on bypass. Major surgical procedures were performed in several patients. The cause of death in the three nonsurvivors was intracranial complications leading to total cerebral infarction. CONCLUSION: A high survival rate can be obtained in adult patients with severe ARDS using ECMO and pressure-supported ventilation with minimal sedation. Surgical complications are amenable to surgical treatment during ECMO. Bleeding problems can generally be controlled but require immediate and aggressive approach. It is difficult or impossible to decide when a lung disease is irreversible, and prolonged ECMO treatment may be successful even in the absence of any detectable lung function.

Body Position Does Not Influence the Location of Ventilator-Induced Lung Injury—Nishimura M, Honda O, Tomiyama N, Johkoh T, Kagawa K, Nishida T. Intensive Care Med 2000 Nov;26(11):1664–1669.

OBJECTIVE: To ascertain whether the locations of ventilator-induced lung injury (VILI) are influenced by body position. DESIGN: Randomized prospective short-term study. SETTING: Animal laboratory at a university school of medicine. INTERVENTIONS: Twelve white rabbits were mechanically ventilated in IMV mode with an infant ventilator (V.I.P. Bird, Bird Products, Palm Springs, Calif., USA). Based on the results of a preliminary study to determine the ventilator settings at which the lungs of rabbits were injured within 5 h in the supine position, the ventilator was set at F_{IO_2} 0.21, at a rate of 30/min, T_I 0.6 s, peak inspiratory pressure 30 cm H_2O, inspiratory flow 10 L/min with no applied positive end-expiratory pressure (PEEP). Six of the animals were tested in the supine position and the other six in the prone position. Respiratory gases were measured and CT scanning was performed every 30 min. The animals were ventilated for 5 h or until pulmonary parenchymal opacification was detected. The lungs were divided into three areas from apex to base and three levels from ventral to dorsal, and the location of opacification was ascribed according to this scheme. After the experiment, the

A new outlook on spirometry from

FUTUREMED

Futuremed's family of spirometers includes the right model for your needs.

Discovery®

- Compact
- Large, real time graphs
- Internal and full page reports
- Data Management Software lets you save patient records on PC
- Ideal for office or mobile testing

SpiroVision-3®

- Converts a Windows® desktop or laptop into a full function spirometer
- Standard port connection - no special adapter needed
- Real-time F/V loops and T/V curves
- Color graphs and printouts
- Reliable, easy to use software
- *NEW* "Bubbles" incentive helps maximize patient results

Futuremed spirometers print full page reports that meet ATS standards for spirometry. They are dependable, full featured and competitively priced. What's more, they let you control cost by using your choice of one-way, bi-directional or filtered mouthpieces.

For more information and a free demonstration call 1-800-222-6780

Futuremed America, Inc.
Granada Hills, CA 91344
818-830-2500, Fax 818-891-4755
www.futuremedamerica.com

Circle 128 on product info card

lungs were excised and examined histologically. MEASUREMENTS AND RESULTS: Parenchymal opacification occurred mainly in the dorsal lung areas. The time from the beginning of ventilation to the appearance of lung damage was 60–120 min in the supine (S) group, and 60–270 min in the prone (P) group, and it was significantly longer in the prone group ($p < 0.01$). We observed diffuse lung damage, including hyaline membrane formation, intra-alveolar edema, and infiltration of inflammatory cells. CONCLUSIONS: Body position affected the time course of the development of VILI, but it did not affect the location.

Hospital-Acquired Pneumonia: Risk Factors, Microbiology, and Treatment—Lynch JP 3rd. Chest 2001 Feb;119(2 Suppl):373S-384S.

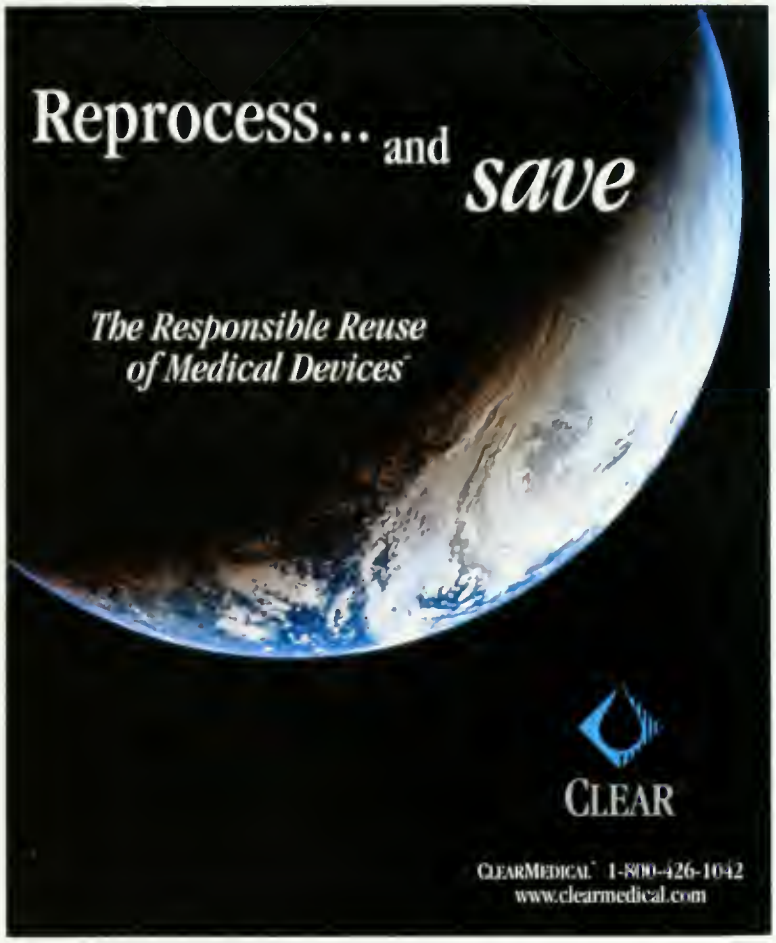
Pneumonia complicates hospitalization in 0.5 to 2.0% of patients and is associated with considerable morbidity and mortality. Risk factors for hospital-acquired pneumonia (HAP) include mechanical ventilation for > 48 h, residence in an ICU, duration of ICU or hospital stay, severity of underlying illness, and presence of comorbidities. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and Enterobacter are the most common causes of HAP. Nearly half of HAP cases are polymicrobial. In patients receiving mechanical ventilation, *P aeruginosa*, Acinetobacter, methicillin-resistant *S aureus*, and other antibiotic-resistant bacteria assume increasing importance. Optimal therapy for HAP should take into account severity of illness, demographics, specific pathogens involved, and risk factors for antimicrobial resistance. When *P aeruginosa* is implicated, monotherapy, even with broad-spectrum antibiotics, is associated with rapid evolution of resistance and a high rate of clinical failures. For pseudomonal HAP, we advise combination therapy with an antipseudomonal beta-lactam plus an aminoglycoside or a fluoroquinolone (eg, ciprofloxacin).

Are Quantitative Cultures Useful in the Diagnosis of Hospital-Acquired Pneumonia?—San Pedro G. Chest 2001 Feb;119(2 Suppl):385S-390S.

Noninvasive and invasive tests have been developed and studied for their utility in diagnosing and guiding the treatment of hospital-acquired pneumonia, a condition with an inherently high mortality. Early empiric antibiotic treatment has been shown to reduce mortality, so delaying this treatment until test results are available is not justifiable. Furthermore, tailoring therapy based on results of either noninvasive or invasive tests has not been clearly shown to affect morbidity and mortality. This may be related to quantitative limitations of these tests or possibly to a high false-negative rate in patients who receive early antibiotic treatment and may therefore have suppressed bacterial counts. Results of these tests, however, do influence treatment. It is therefore hoped that they may ultimately provide a rational basis for making therapeutic decisions. In the future, outcomes research should be a part of large-scale clinical trials, and noninvasive and invasive tests should be incorporated into the design in an attempt to provide a better understanding of the value of such tests.

Guidelines and Critical Pathways for Severe Hospital-Acquired Pneumonia—Fiel S. Chest 2001 Feb;119(2 Suppl):412S-418S.

Hospital-acquired pneumonia (HAP) is associated with high morbidity and mortality. Early, appropriate, and adequate empiric therapy can increase the chance of survival. In 1995, the American Thoracic Society provided guidelines for the initial treatment of immunocompetent HAP patients, which is one of the principal HAP management approaches available to physicians today. However, these guidelines have several important limitations, including a lack of recommendations for duration of therapy and no recognition of newer drugs such as cefepime, trovafloxacin, and meropenem. Furthermore, they fail to distinguish among similar compounds (ie, beta-lactam/beta-lactamase inhibitor combina-



Circle 123 on product info card

tions) or to recommend specific antibiotics. The clinician using these guidelines needs to address local patterns of antimicrobial resistance, especially in ICUs. Effective computerized antibiotic management programs that incorporate information on local patterns of antimicrobial resistance can assist physicians in empiric therapy decision making, improve patient quality of care, and reduce medical costs.

Implementation of Strategies to Control Antimicrobial Resistance—Murthy R. Chest 2001 Feb;119(2 Suppl):405S-411S.

Antimicrobial resistance has emerged as a major public health issue in recent years. A steady increase in resistance continues despite the introduction of new antibiotics, and resistant bacteria have been associated with increased patient morbidity and mortality as well as with increased costs. Addressing the problem of antimicrobial resistance requires both infection control and regulation of antibiotic use; addressing either alone is insufficient. Mounting evidence shows that control of the use of broad-spectrum antibiotics (especially vancomycin and third-generation cephalosporins) and implementation of infection control measures can result in decreased incidence of antibiotic-resistant bacteria such as vancomycin-resistant enterococci and extended-spectrum beta-lactamase-producing *Escherichia coli* and Klebsiella. Recent reports from professional organizations and a consensus of experts have outlined strategies for the control of resistance in hospitals, with specific measures identified for antibiotic control and infection control. These reports have emphasized the importance of a multidisciplinary approach in tackling this problem in hospitals and have suggested that a quality-improvement model be used to address antimicrobial resistance. A close collaboration among the disciplines of infectious diseases, microbiology, hospital epidemiology, pharmacy, and nursing, with particular emphasis in ICUs, and with strong support from hospital leadership, can result in an effective program that can be readily incorporated into the quality-improvement goals of any health-care organization.

Resistance Patterns Among Nosocomial Pathogens: Trends over the Past Few Years—Jones RN. Chest 2001 Feb;119(2 Suppl):397S-404S.

Multiple surveillance studies have demonstrated that resistance among prevalent pathogens is increasing at an alarming rate, leading to greater patient morbidity and mortality from nosocomial infections. Among Gram-positive organisms, the most important resistant pathogens are methicillin- (oxacillin-)resistant *Staphylococcus aureus*, beta-lactam-resistant and multidrug-resistant pneumococci, and vancomycin-resistant enterococci. Important causes of Gram-negative resistance include extended-spectrum beta-lactamases (ESBLs) in *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis*, high-level third-generation cephalosporin (Amp C) beta-lactamase resistance among Enterobacter species and *Citrobacter freundii*, and multidrug-resistance genes observed in *Pseudomonas aeruginosa*, Acinetobacter, and *Stenotrophomonas maltophilia*. In selecting an empiric treatment for a nosocomial infection, one should consider the prevalent resistance patterns. Antimicrobials used for the treatment of nosocomial infections should be effective against any likely resistant pathogens and should not further promote the development of resistance. Recent data suggest that because of ESBLs and high-level amp C beta-lactamase resistances, use of third-generation cephalosporins may be ineffective in many patients with nosocomial infections. In addition, use of these agents may allow overgrowth of inherently resistant enterococci. The role of fluoroquinolones in the empiric treatment of nosocomial infections is also being limited by new resistance patterns and increasing resistance levels. Available antimicrobials with good activity against many resistant pathogens include the carbapenems, piperacillin/tazobactam, and cefepime. In addition, several new agents with good activity against Gram-positive organisms are in development or have been recently re-

leased. Appropriate antimicrobial selection, surveillance systems, and effective infection-control procedures are key partners in limiting antimicrobial-resistant pathogen occurrence and spread.

Cerebrovenous Oxygen Saturation Monitoring: Practical Considerations and Clinical Relevance—Macmillan CS, Andrews PJ. Intensive Care Med 2000 Aug;26(8):1028–1036.

Measurement of the saturation of brain effluent blood gives a global estimate of cerebral oxygenation. It may provide clinicians with information to assist in reducing secondary insults to the brain with potential benefits to a range of patients with actual or potential acute brain injury such as trauma and cardiac bypass procedures. The technology to continuously measure this variable is simple to use but requires attention to detail; it is limited in its ability to detect discrete regions of ischaemia or hyperaemia unless these are of sufficient magnitude to influence the saturation of brain effluent blood. There are few complications that result from this invasive technique and they are usually of a minor nature. The technique also enables research opportunities from the ability to sample blood as it leaves the cranium. Poor outcomes are seen in patients with traumatic brain injury who exhibit either reduced or increased cerebrovenous oxygen saturation and it remains to be seen if detection and correction of these anomalies will produce patient benefits.

Regional Distribution of Gas and Tissue in Acute Respiratory Distress Syndrome. II. Physiological Correlations and Definition of an ARDS Severity Score. CT Scan ARDS Study Group—Rouby JJ, Puybasset L, Cluzel P, Richecoeur J, Lu Q, Grenier P. Intensive Care Med 2000 Aug;26(8):1046–1056.

OBJECTIVES: (a) To assess whether differences in lung morphology observed in patients with adult respiratory distress syndrome (ARDS) are associated with differences in cardiorespiratory parameters, lung mechanics, and outcome. (b) To propose a new ARDS Severity Score to identify patients with a high mortality risk. DESIGN: Prospective study over a 53-month period. SETTING: Fourteen-bed surgical intensive care unit of a university hospital. PATIENTS AND PARTICIPANTS: Seventy-one consecutive patients with early ARDS. MEASUREMENTS AND RESULTS: Cardiorespiratory parameters were measured using a Swan-Ganz catheter, the pressure-volume (PV) curve was measured using the gross syringe method, and fast spiral computed tomography (CT) was performed. Patients with diffuse attenuations (n = 16) differed from patients with lobar attenuations (n = 26) regarding: (a) mortality rate (75% vs. 42%, p = 0.05), (b) incidence of primary ARDS (82% vs. 50%, p = 0.03), (c) respiratory compliance (47 ± 12 vs. 64 ± 16 mL per cm H_2O^{-1} p = 0.04), and (d) lower inflexion point (8.4 ± 2.0 vs. 4.6 ± 2.0 cm H_2O, p = 0.001). A third group of patients with patchy attenuations (n = 29) had a mortality rate of 41 %, a respiratory compliance of 56 ± 18 mL per cm H_2O^{-1} and a lower inflexion point of 6.3 ± 2.7 cm H_2O. The bedside chest radiograph accurately assessed lung morphology in only 42% of the patients. In contrast to the scores based on the bedside chest radiograph, a new ARDS Severity Score based on CT lung morphology and cardiorespiratory parameters identified a subgroup of patients with a high mortality rate (≥ 60%). CONCLUSIONS: In patients with ARDS, differences in lung morphology are associated with differences in outcome and lung mechanics. A new ARDS Severity Score based on CT lung morphology and cardiorespiratory parameters accurately identified patients with the most severe forms of ARDS and a mortality rate above 60%.

Anterior Magnetic Phrenic Nerve Stimulation: Laboratory and Clinical Evaluation—Polkey MI, Duguet A, Luo Y, Hughes PD, Hart N, Hamnegard CH, et al. Intensive Care Med 2000 Aug;26(8):1065–1075.

OBJECTIVE: Anterior magnetic stimulation (aMS) of the phrenic nerves is a new method for the assessment of diaphragm contractility that might have particular applications for the clinical assessment of critically ill patients who are commonly supine. DESIGN: We compared aMS with existing techniques for measurement of diaphragm weakness and fatigue in 10 normal subjects, 27 ambulant patients with suspected diaphragm weakness and 10 critically ill patients. SETTING: Laboratory and intensive care unit of two university hospitals. RESULTS: Although aMS was not demonstrably supramaximal in normal subjects, the mean value of twitch transdiaphragmatic pressure (Tw Pdi) obtained at 100% of stimulator output, 23.7 cm H_2O, did not differ significantly from that obtained with bilateral supramaximal electrical stimulation (ES), 24.9 cm H_2O, or bilateral anterior magnetic phrenic nerve stimulation (BAMPS), 27.3 cm H_2O. A fatiguing protocol produced a 20% fall in aMS-Tw Pdi and a 19% fall in BAMPS-Tw Pdi; the fall in aMS-Tw Pdi correlated with the fall in BAMPS-Tw Pdi (r^2 = 0.84, p = 0.03) indicating that aMS can detect diaphragm fatigue. In ambulant patients aMS agreed closely with existing measures of diaphragm strength. The maximal sniff Pdi correlated with both the aMS-Tw Pdi (r^2 = 0.60, p < 0.0001) and the BAMPS-Tw Pdi (r^2 = 0.65, p < 0.0001) and the aMS-Tw Pdi was a mean (SD) 2.2 (4.3) cm H_2O less than BAMPS-Tw Pdi. In addition, aMS correctly identified diaphragm dysfunction in patients studied on the ICU. CONCLUSIONS: We conclude that aMS is of clinical value for the investigation of suspected diaphragm weakness.

Cost Analysis of Plasma-Exchange Therapy for the Treatment of Guillain-Barré Syndrome. French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome—Esperou H, Jars-Guincestre MC, Bolgert F, Raphael JC, Durand-Zaleski I. Intensive Care Med 2000 Aug; 26(8):1094–1100.

OBJECTIVE: To undertake a cost analysis of therapeutic strategies with plasma exchange (PE) for the treatment of patients with Guillain-Barré syndrome. DESIGN: A randomized clinical trial including 556 patients with Guillain-Barré syndrome. We demonstrated that in the group with mild disease (walking possible) two PEs were more effective than none in shortening the time to beginning motor recovery. In the groups with moderate disease (walking impossible) and or severe disease (mechanically ventilated patients) four sessions were more effective than two and no more effective than six in shortening the time to recovery of walking with assistance and for the recovery rate of full muscle strength within 1 year. Data on outcomes and costs was collected. Complete cost data were available on 546 from the 556 patients of the trial. Costs were estimated from the viewpoint of the healthcare system and computed over a 1-year period. Because the analysis of medical outcomes did not show any difference regarding mortality but only on intermediate short-term and long-term outcomes, we carried out a cost minimization analysis. RESULTS: In two groups a dominant strategy appeared, with greater efficacy and lower costs in the two-PE arm for the mild group: 21,353 euros vs. 38,753 euros and in the four-PE arm in the moderate group: 59,480 euros vs. 80,737 euros. In the severe group four PEs were as efficient and somewhat less expensive than six: 57,621 vs. 61,056 euros. CONCLUSION: The treatment of Guillain-Barré syndrome by PE at the onset of disease appears to have medical justification. The least expensive strategies are either more or equally efficient as more expensive strategies.

Early Translaryngeal Tracheostomy in Patients with Severe Brain Damage—Stocchetti N, Parma A, Songa V, Colombo A, Lamperti M, Tognini L. Intensive Care Med 2000 Aug;26(8):1101–1107.

OBJECTIVES: To describe the effects of early translaryngeal tracheostomy on intracranial pressure (ICP), cerebral perfusion pressure (CPP), and jugular bulb saturation (SjO_2); to identify the main mechanisms affecting ICP during tracheostomy; and to evaluate the long-term effects of tracheostomy on tracheal anatomy and function. DESIGN: Prospec-

MARK YOUR CALENDARS!
FUTURE AARC CONGRESSES

December 1-4, 2001
San Antonio, Texas

October 5-8, 2002
Tampa, Florida

December 8-11, 2003
Las Vegas, Nevada

December 4-7, 2004
New Orleans, Louisiana

tive, observational, clinical study. SETTING: Neurosurgical intensive care unit in a teaching hospital. PATIENTS: 20 patients admitted to the ICU because of head injury, subarachnoid hemorrhage, or brain tumor with a Glasgow Coma Scale less than 8. INTERVENTIONS: Patients underwent translaryngeal tracheostomy under strict neuromonitoring. MEASUREMENTS AND RESULTS: ICP rose significantly ($p < 0.05$) at the critical time of cannula placement while all other parameters remained stable. At this time five patients suffered intracranial hypertension (ICP > 20 mm Hg). In one of them CPP dropped below 60 mm Hg. Arterial CO_2 tension (P_{aCO_2}) did not rise significantly. No other major complications were recorded during the procedures. Three months after tracheostomy normal findings were detected by tracheoscopy in all cases (11 patients could be examined). CONCLUSIONS: Translaryngeal tracheostomy, performed in selected patients when the risk of intracranial hypertension was reduced to the minimum, was well tolerated in the majority of cases and did not induce persistent intracranial disorders. However, ICP is affected by tracheostomy, and careful monitoring and patient selection is necessary. At follow-up no severe anatomical or functional damage was detected.

Blood in the Gastrointestinal Tract Delays and Blunts the $P_{i\,CO_2}$ Response to Transient Mucosal Ischaemia—Venkatesh B, Morgan TJ. Intensive Care Med 2000 Aug;26(8):1108–1115.

OBJECTIVE: To determine whether the presence of blood in the gastrointestinal tract impairs the detection of splanchnic mucosal ischaemia by reducing the rate and magnitude of rise in gut luminal P_{CO_2}. DESIGN: Prospective observational study. SETTING: University Research Laboratory. SUBJECTS: Four adult male Wistar rats with four controls from a concurrent study. INTERVENTIONS: Four adult male Wistar rats were anaesthetised with sodium pentobarbitone and ventilated with oxygen and isoflurane to an initial P_{aCO_2} of 30–40 torr. Electrochemical-fiberoptic gas sensors inserted into silastic tubing placed in the ileal lumen measured luminal P_{CO_2} at 1-s intervals. Distal aortic pressure was monitored continuously. Six 2-min episodes of aortic hypotension were induced in each rat to a mean pressure of 30 mm Hg by intermittent elevation of a silk sling placed around the proximal aorta. Before the last three episodes in each rat 0.75–1.0 mL blood was injected into the ileal lumen via a 25-gauge needle. Four control rats from a concurrent experiment were treated in an identical fashion except that the rats were subjected to five ischaemic episodes, and there was no intraluminal injection of blood, although a 20-gauge cannula was placed in the proximal ileal lumen. MEASUREMENTS AND MAIN RESULTS: The presence of blood in the lumen significantly decreased the ischaemic ΔP_{CO_2} response from 33 ± 8 to 15 ± 4 torr ($p < 0.001$) and also significantly increased the peak response time from 188 ± 12 to 227 ± 24 s ($p < 0.001$). The corresponding measurements in the concurrent controls differed only from the values after blood injection in the experimental group. CONCLUSIONS: In this animal model the presence of intraluminal blood significantly delayed the rate and the amplitude of luminal P_{CO_2} increases in response to transient ischaemia. This raises questions about the validity of luminal CO_2 measurements as an indicator of splanchnic ischaemia in the presence of gastrointestinal haemorrhage.

Theoretical and Experimental Comparison of Constant Inspired Concentration and Pulsed Delivery in NO Therapy—Heinonen E, Hogman M, Merilainen P. Intensive Care Med 2000 Aug;26(8):1116–1123.

OBJECTIVE: Inhaled NO therapy of artificially ventilated patients has been established as being based on constant inspired concentration of NO. In this study a new volumetrically controlled pulsed NO delivery mode is compared with the established concentration-based concept. DESIGN: To evaluate the relationship between NO delivery parameters, alveolar NO fraction, and patient uptake, a mathematical lung model was

Deep in the Heart of Texas...

in the midst of its bluebonnet-bedecked Hill Country is the city of San Antonio, one of the country's truly unique cities. Explore the city and its countryside, while you also explore the newest and best in respiratory care at the 47th International Respiratory Congress.

Learn more about San Antonio's offerings at www.sanantoniocvb.com

47th International Respiratory Congress

December 1-4, 2001 • San Antonio, Texas USA

Experience the Best of the Science, Tradition, and Future of Respiratory Care

- **28th Annual Donald F Egan Scientific Lecture**
  COPD — On the Exponential Curve of Progress
  John Heffner MD, of the Medical University of South Carolina, will address COPD and its growing significance for respiratory therapists.

- **17th Annual Phil Kittredge Memorial Lecture**
  Mechanical Ventilation: How Did We Get Here and Where Are We Going?
  Among therapists, Rich Branson RRT FAARC, of the University of Cincinnati Medical Center, is well recognized as an authority and visionary when it comes to mechanical ventilation.

- **27th Annual Open Forum**
  Hundreds of original research papers will be showcased over the four days of the Congress, reviewing the latest in pediatric, adult, critical care, home care, and education. (You can still submit your research project - deadline July 31). Learn about cutting-edge research in the Open Forum and see the latest technology in the Exhibit Hall.

- **17th Annual New Horizons Symposium**
  This year the topic is airway clearance techniques. This featured symposium attracts an audience of hundreds who come to immerse themselves in the most thorough review of a clinical topic.

Secure your early bird low-cost registration fee now. Register online at www.aarc.org. Also, continue checking the AARC web site for the latest information on the Congress.

The AARC's International Respiratory Congress is the gold standard of respiratory care meetings. The Congress boasts:

- The lowest cost of continuing education per credit of any show, anywhere.
- The largest and most impressive Exhibit Hall with the most vendors, where you can make your best deals on major purchases AT THE SHOW!
- The largest gathering of respiratory care experts and opinion-makers in the world.
- The most diverse and most dynamic series of lectures.
- The most opportunities for YOU to participate in your profession through research and networking.

TRAVEL TIP:
Trails of Texas

www.texas-on-line.com/graphic/trail.htm

created where NO delivery can be simulated in varying ventilator settings, delivery modes, and lung properties. This model and the efficacy of pulsed delivery in inducing pulmonary capillary vasodilatation were examined experimentally. SETTING: Animal laboratory, Department of Medical Sciences, Clinical Physiology. SUBJECTS: The experimental study was performed with nine pigs of mixed breed weighing 25–35 kg. INTERVENTIONS: The pigs were anaesthetised and artificially ventilated. Pulmonary vasoconstriction was induced by hypoxia. NO was delivered periodically in the various delivery modes. MEASUREMENTS AND RESULTS: In simulation, in all delivery modes the NO uptake was found to be dependent on the ventilator settings and the volume of the dead space. Measured from pulmonary artery pressure, the pulsed delivery was as effective in reducing the induced pulmonary vasoconstriction as the constant inspired concentration delivery. The amount of NO that could reduce the vasoconstriction back to baseline was 105 nmol × min^{-1}. By delivering in the early part of the inspiration, ambient contamination by the exhaust gas is avoided. The expired NO values obtained in the simulation and the experiments were equal. Based on the simulation, the alveolar NO fraction and the NO uptake depend on the ventilator settings and the dead space in both volumetric- and concentration-based delivery. CONCLUSIONS: With pulsed delivery, a therapeutic effect comparable to constant inspired concentration delivery is achieved, NO gas is used more effectively, and environmental exhausts are reduced. The theoretical model shows that the NO delivery does not predict alveolar NO fraction and the NO uptake. However, it still remains an open question if the online measurement of these parameters would provide useful information, having added value in predicting and controlling the efficacy of the NO treatment.

Inhaled Nitric Oxide in Neonates with Persistent Pulmonary Hypertension—Tworetzky W, Bristow J, Moore P, Brook MM, Segal MR, Brasch RC, et al. Lancet 2001 Jan 13;357(9250):118–120.

To investigate the oxygenation and haemodynamic dose response to inhaled nitric oxide in neonates with persistent pulmonary hypertension (PPHN), we gave seven neonates nitric oxide and measured directly pulmonary arterial pressure. Inhaled nitric oxide produced peak improvement in oxygenation at 5 parts per million (ppm) whereas peak improvement in the pulmonary-to-systemic arterial pressure ratio did not occur until a nitric oxide dose of 20 ppm, which suggests that an Initial dose of 20 ppm is optimum for the treatment of PPHN.

Relationship Between Smoking and Weight Control Efforts Among Adults in the United States—Wee CC, Rigotti NA, Davis RB, Phillips RS. Arch Intern Med 2001 Feb 26;161(4):546–550.

BACKGROUND: The effect of weight control concerns on smoking among adults is unclear. We examined the association between smoking behavior and weight control efforts among US adults. METHODS: A total of 17 317 adults responded to the Year 2000 Supplement of the 1995 National Health Interview Survey (83% combined response rate). Respondents provided sociodemographic and health information, including their smoking history and whether they were trying to lose weight, maintain weight, or gain weight. RESULTS: Rates of smoking were lower among adults who were trying to lose or maintain weight than among those not trying to control weight (25% vs 31%; $p<0.001$). After adjustment for sex, race, education, income, marital status, region of the country, and body mass index, the relationship between trying to lose weight and current smoking varied according to age. Among adults younger than 30 years, those trying to lose weight were more likely to smoke currently (odds ratio, 1.36 [95% confidence interval, 1.09–1.70]), whereas older adults trying to lose weight were as likely or less likely to smoke compared with adults not trying to control weight. After adjustment, smokers of all ages who were trying to lose weight were more likely to express a desire to quit smoking. Results were similar after stratification by sex and body mass index. CONCLUSIONS: Adults younger than 30 years are more likely to smoke if they are trying to lose weight. However, smokers of all ages who are trying to lose weight are more likely to want to stop smoking. Patients' weight control efforts should not discourage clinicians from counseling about smoking cessation. Education about smoking and healthy weight control methods should target young adults.

Diagnosis of Pulmonary Alveolar Proteinosis: Usefulness of Papanicolaou-Stained Smears of Bronchoalveolar Lavage Fluid—Chou CW, Lin FC, Tung SM, Liou RD, Chang SC. Arch Intern Med 2001 Feb 26;161(4):562–566.

BACKGROUND: The globules (stained green, orange, or orange in the center coated with a green rim) seen in Papanicolaou-stained smears of bronchoalveolar lavage fluid are suggested to be characteristic of pulmonary alveolar proteinosis (PAP). OBJECTIVE: To evaluate the usefulness of Papanicolaou-stained smears of bronchoalveolar lavage fluid in aiding a diagnosis of PAP. METHODS: Papanicolaou-stained smears of bronchoalveolar lavage fluid obtained from 7 patients (5 idiopathic, 2 secondary) with PAP were evaluated. To serve as controls, the smears of 11 normal subjects and 128 patients with other pulmonary disorders were also examined. The findings on the presence and number of globules were recorded. To differentiate PAP from other pulmonary disorders, the highest globule value obtained from the control group was chosen as the cutoff point. RESULTS: The characteristic globules were not found in normal subjects and only found in 6 of 128 patients with other pulmonary disorders. Their clinical diagnoses were Sjogren syndrome in 2 cases; polymyositis, idiopathic pulmonary fibrosis, asbestosis, and hypersensitivity pneumonitis in 1 case each. The numbers of globules in these 6 patients were 1, 3, 17, 7, 3, and 2. In contrast, more than 100 globules were found in all patients with PAP. The number of globules was highly sensitive and specific in aiding a diagnosis of PAP when the cutoff value was set at 18. CONCLUSION: The globules seen in Papanicolaou-stained smears of bronchoalveolar lavage fluid may be valuable in aiding a diagnosis of PAP, especially when the number of globules is more than 18.

The Impact of the Introduction of a Rapid D-Dimer Assay on the Diagnostic Evaluation of Suspected Pulmonary Embolism—Goldstein NM, Kollef MH, Ward S, Gage BF. Arch Intern Med 2001 Feb 26; 161(4):567–571.

BACKGROUND: Rapid D-dimer assays are being used in the diagnostic evaluation of suspected pulmonary embolism (PE). Although this hypothesis is anticipated to decrease the use of ventilation-perfusion (V/Q) scans and other diagnostic tests for PE, it has not been tested in a "real-world" environment. SUBJECTS AND METHODS: A randomized prospective trial was conducted on 470 of the 5390 enrolled patients aged 60 years and older who had previously undergone any diagnostic tests for PE at an urban teaching hospital. The use of D-dimer as part of the diagnostic evaluation for PE was promulgated in the 2 randomly chosen intervention firms. The remaining 2 firms served as controls. MAIN OUTCOME MEASURES: The number of V/Q scans, spiral computed tomographic scans, and pulmonary angiograms performed. Secondary outcomes included mortality and thromboembolic or bleeding events during 3 months of follow-up. RESULTS: Of the 470 inpatients who underwent evaluation for PE on a per PE workup basis, fewer V/Q scans were performed in the intervention firms (63.8% vs 81.3%; $p<0.01$). However, the number of patients evaluated for PE nearly doubled in the intervention firms (304 vs 166; $p<0.01$), so that more V/Q scans were performed in the intervention than in the control firms (194 vs 135; $p<0.01$). Ninety-four patients from the control firms and 160 patients from the intervention firms were diagnosed and treated for venous thromboembolic disease ($p<0.01$). There were no differences in secondary outcomes during the 3-month follow-up. CONCLUSIONS: The introduction of a rapid D-dimer assay increased the number of V/Q scans

performed because the number of patients screened for PE increased. A larger number of patients in the intervention firms were diagnosed as having venous thromboembolic disease (PE and/or deep vein thrombosis). There were no perceived changes in mortality or venous thromboembolic events during the 3-month follow-up.

The Clinical Features of Severe Community-Acquired Pneumonia Presenting As Septic Shock. Norasept II Study Investigators—Marik PE. J Crit Care 2000 Sep;15(3):85–90.

PURPOSE: The purpose of this article was to determine the outcome, clinical and prognostic features, and microbiology of a large group of patients with community-acquired pneumonia (CAP) presenting in septic shock. MATERIALS AND METHODS: The placebo limb of the Norasept II database was examined. Data were collected on patients in septic shock with a diagnosis of CAP who presented to a participating site from home. RESULTS: One hundred and forty-eight patients met the study criteria. The 28-day survival was 53%. One hundred and four pathogens were isolated from 77 (52%) patients with 24 (16%) patients having polymicrobial infections. The most common pathogen was *Streptococcus pneumoniae* (19%), followed by *Staphylococcus aureus* (18%), *Haemophilus influenzae* (14%), *Klebsiella pneumoniae* (11%), and *Pseudomonas aeruginosa* (7%). Infection with *P aeruginosa* or Acinetobacter species carried a very high mortality (82%). The only clinical variables recorded in the database that could identify patients with pseudomonas or acinetobacter infection was a history of alcohol abuse. Comorbidities were present in 74% of patients, involving predominantly the cardiorespiratory system. Logistic regression analysis demonstrated APACHE II score and serum interleukin 6 (IL-6) concentration to be significant independent predictors of mortality. Patients with pseudomonas or acinetobacter infection had significantly higher IL-6 levels and significantly lower tumor necrosis factor alpha levels when compared with the rest of the cohort of patients. CONCLUSION: A diverse spectrum of both Gram-positive and Gram-negative pathogens were implicated in patients with CAP presenting in septic shock, necessitating broad spectrum empiric antimicrobial coverage. This coverage should include antipseudomonal activity, particularly in alcoholic patients. Severity of illness (APACHE II score) and IL-6 levels were important prognostic factors. Infection with *P aeruginosa* and Acinetobacter species carried a very high mortality.

Acute Respiratory Distress Syndrome: Resource Use and Outcomes in 1985 and 1995, Trends in Mortality and Comorbidities—Pola MD, Navarrete-Navarro P, Rivera R, Fernandez-Mondejar E, Hurtado B, Vazquez-Mata G. J Crit Care 2000 Sep;15(3):91–96.

PURPOSE: The purpose of this study was to compare resource consumption and mortality between (ARDS) patients with adult respiratory distress syndrome treated at our center in 1985 (45 patients) and those treated in 1995. MATERIALS AND METHODS: This was a retrospective observational study, considering trauma and nontrauma ARDS separately. We recorded severity index scores (APACHE III), infectious complications and multiorgan failure, intensive care unit (ICU) resource consumption (TISS 28), length of stay, time on mechanical ventilation, and ICU mortality. RESULTS: We found no variation in overall ARDS mortality and no reduction in mortality in the ARDS trauma group (43.5% in 1985 vs. 38.5% in 1995, not significant) but a significant increase in mortality among nontrauma septic ARDS patients (68.2% vs. 82.9%, $p < 0.001$), largely attributable to the new comorbidities of human immunodeficiency virus (HIV) infection and hematologic malignancy. TISS-28 showed an overall reduction over this time period (49.7 ± 6.6 vs. 38.3 ± 9.7, $p < 0.001$), due to fewer monitoring measures, particularly a lower use of pulmonary artery catheter. There were no overall changes in length of stay or days on mechanical ventilation between 1985 and 1995, but these variables did increase among the trauma subgroup. CONCLU-

SATELLITE SPIROMETER

THE POWER OF DESKTOP SIZE SPIROMETRY IN THE PALM OF YOUR HAND

• Accurate • Hygienic • Economical
• User Friendly • Fully Reimbursable

The Satellite Spirometer is the only full function, handheld spirometer that meets all recognized standards, offering the power and convenience of the Base Station.

SPECIAL FEATURES INCLUDE:

- Handheld *cordless* unit weighs only 1 pound
- *Does not* require external printer or PC connection
- Complete printout in only 8 seconds
- *Least expensive* disposable sensor available (99¢)
- **Cost effective** - Don't get trapped purchasing a cheap spirometer that requires expensive sensors. The low cost of the Satellite sensor can save thousands of dollars every year in disposable costs.

Call for a free demonstration today!

(800) 323-7336

JONES Medical Instrument Co.
200 Winsdor Drive • Oak Brook, IL 60523
(630) 571-1980 FAX (630) 571 2023
www.jonesmedical.com

Circle 140 on product info card

SION: In our setting, mortality remained constant from 1985 to 1995 among ARDS trauma patients but not among nontrauma ARDS patients because of the new case-mix of the latter population, which now includes HIV and other immunodepressed patients.

Partial Liquid Ventilation Shows Dose-Dependent Increase in Oxygenation with PEEP and Decreases Lung Injury Associated with Mechanical Ventilation—Suh GY, Chung MP, Park SJ, Koh Y, Kang KW, Kim H. J Crit Care 2000 Sep;15(3):103–112.

PURPOSE: The purpose of this article is to evaluate the effect of positive end-expiratory pressure (PEEP) during partial liquid ventilation (PLV) and to investigate if lung damage associated with mechanical ventilation can be reduced by PLV. MATERIALS AND METHODS: Twenty-two New-Zealand white rabbits were ventilated in pressure-controlled mode maintaining constant tidal volume (10 mL/kg). Lung injury was induced by repeated saline lavage (P_{aO_2} < 100 mm Hg).Two incremental PEEP steps maneuvers (IPSMs) from 2 to 10 cm H_2O in 2 cm H_2O steps were performed sequentially. The control group received the first IPSM in the supine position and were turned prone for the second IPSM. In the PLV group (n = 7), 12 mL/kg of perfluorodecalin was instilled after lung injury before the two IPSMs. The early prone group (n = 7) received both IPSMs in the prone position. Parameters of gas exchange, lung mechanics, and hemodynamics as well as pathology were examined. RESULTS: During the first IPSM, the PLV group showed a significant increase in P_{aO_2} after instillation of perfluorodecalin ($p < 0.05$) and then showed a dose-dependent increase in P_{aO_2} with PEER. The control and EP groups showed improvement in P_{aO_2} only at higher PEEP, eventually showing no intergroup differences at PEEP of 10 cm H_2O. During the second IPSM only the PLV group retained its ability to increase P_{aO_2} to the level obtained during the first IPSM ($p < 0.05$ compared with control and EP groups). During the first IPSM all three groups showed increasing trend in static compliance (Cst) with PEEP peaking at PEEP of 8 cm H_2O. During the second IPSM, only the PLV group showed increase in static compliance with PEEP ($p < 0.05$ compared with other groups). Lung histology revealed significantly less hyaline membrane formation in the PLV group ($p < 0.05$). CONCLUSION: PLV shows dose-dependent increase in oxygenation with PEEP and may reduce lung damage associated with mechanical ventilation.

Design Strategies for Longitudinal Spirometry Studies: Study Duration and Measurement Frequency—Wang ML, Gunel E, Petsonk EL. Am J Respir Crit Care Med 2000 Dec;162(6):2134–2138.

Measuring the longitudinal change in FEV_1 is useful for assessing the adverse effects of respiratory exposures and pulmonary diseases. Investigators seek to estimate the "true" mean FEV_1 slope (μ_β) of an infinite population. The difference between the estimated mean FEV_1 slope ($\hat{\mu}_\beta$) and the true mean slope, resulting from biological variation and measurement errors, can be minimized by increasing the number of subjects (N), years of follow-up (D), or the frequency of measurements (P). We defined maximum error e_{max} such that $P[\ \mu_\beta - \mu_\beta\ \leq e_{max}] = 0.95$, and thus e_{max} is one-half the width of the 95% confidence interval for μ_β. We computed the values of e_{max} on the basis of actual data obtained from 160 coal miners and working nonminers who had completed 11 spirometry measurements, using recommended equipment and procedures, at 6-mo intervals over 5 yr. Individual 5-yr FEV_1 slopes (ΔFEV_1) were calculated by linear regression. For a range of values of N, D, and P, tables are provided for e_{max}, the magnitude of detectable differences in ΔFEV_1 between two groups, and the recommended number of subjects needed in each of two groups to reliably detect the anticipated differences in ΔFEV_1. The tables provide unique guidance for investigators in selecting among various study design options.

End-Tidal CO_2 Pressure Determinants During Hemorrhagic Shock—Dubin A, Murias G, Estenssoro E, Canales H, Sottile P, Badie J, et al. Intensive Care Med 2000 Nov;26(11):1619–1623.

OBJECTIVES: To examine the relationship between end-tidal CO_2 (P_{ETCO2}) and its physiological determinants, pulmonary blood flow (cardiac output, CO) and CO_2 production (V CO_2), in a model of hemorrhagic shock during fixed minute ventilation. DESIGN AND SETTING: Prospective, observational study in a research laboratory at a university center. SUBJECTS AND INTERVENTIONS: Six anesthetized, intubated, and mechanically ventilated mongrel dogs. Progressive stepwise bleeding. MEASUREMENTS AND RESULTS: We continuously measured P_{ETCO2} with a capnograph, pulmonary artery blood flow with an electromagnetic flow probe, arterial oxygen saturation (S_{aO_2}) with a fiberoptic catheter, and oxygen consumption (VO_2) and VCO_2 by expired gases analysis. Oxygen delivery (DO_2) was continuously calculated from pulmonary blood flow and S_{aO_2}. We studied the correlation of P_{ETCO2} with CO and VCO_2 in each individual experiment. We also calculated the critical point in the relationships P_{ETCO2}/ DO_2 and VO_2/DO_2 by the polynomial method. As expected, P_{ETCO2} was correlated with CO. The best fit was logarithmic in all experiments (median $r^2 = 0.90$), showing that P_{ETCO2} decrease is greater in lowest flow states. P_{ETCO2} was correlated with VCO_2, but the best fit was linear (median $r^2 = 0.77$). Critical DO_2 for P_{ETCO2} and VO_2 was 8.0 ± 3.3 and 6.3 ± 2.5 mL × min $^{-1}$ kg $^{-1}$, respectively (NS). CONCLUSIONS: Our data reconfirm the relationship between P_{ETCO2} and CO during hemorrhagic shock. The relatively greater decrease in P_{ETCO2} at lowest CO levels could represent diminished CO_2 production during the period of VO_2 supply dependency.

Linear and Nonlinear Analysis of Pressure and Flow During Mechanical Ventilation—Vassiliou MP, Petri L, Amygdalou A, Patrani M, Psarakis C, Nikolaki D, et al. Intensive Care Med 2000 Aug;26(8):1057–1064.

OBJECTIVE: Linear modeling as a method of exploring respiratory mechanics during mechanical ventilation, was compared to nonlinear modeling for flow dependence of resistance in three distinct groups of patients, those with: (a) normal respiratory function (NRF), (b) chronic obstructive pulmonary disease (COPD), or (c) adult respiratory distress syndrome (ARDS). DESIGN AND PATIENTS: Airways opening pressure (Pao), flow (Y), and volume (V) signals were recorded in 32 ICU mechanically ventilated patients, under sedation and muscle relaxation (10 NRF, 11 COPD, 11 ARDS). All patients were ventilated with controlled mandatory ventilation mode at three levels of end-expiratory pressure (PEEPe): 0, 5, and 10 hPa. Data were analyzed according to: (a) Pao = PE + Ers V + Rrs Y and (b) Pao = PE + Ers V + k1Y + k2?Y?Y; where Ers and Rrs represent the intubated respiratory system (RS) elastance and resistance, k1 and k2 the linear and the nonlinear RS resistive coefficients, and PE the end-expiratory pressure. The model's goodness of fit to the data was evaluated by the root mean square difference of predicted minus measured Pao values. RESULTS: NRF data fit both models well at all PEEPe levels. ARDS and particularly COPD data fit the nonlinear model better. Values of k2 were often negative in COPD and ARDS groups, and they increased in parallel with PEEPe. A gradual increase in PEEPe resulted in better fit of ARDS and COPD data to both models. CONCLUSIONS: The model of Y dependence of resistance is more suitable for the ARDS and particularly the COPD groups. PEEP tends to diminish the Y dependence of respiratory resistance during the respiratory cycle, particularly in the COPD group, probably through an indirect effect of the increased lung volume.

Management of Dyspnea in Patients With Far-Advanced Lung Disease: "Once I Lose It, It's Kind of Hard to Catch It."—Luce JM, Luce JA. JAMA 2001 Mar 14;285(10):1331-1337.

Dyspnea is a common problem among patients with interstitial fibrosis, lung cancer, cystic fibrosis, and chronic obstructive pulmonary disease. The slow but steady progression of such diseases, often punctuated by acute exacerbations or secondary illnesses, can lead to decision-making dilemmas among patients and their caregivers, such as when to accept mechanical ventilation, when to forgo aggressive therapies, and when to make formal end-of-life care plans. Two cases, a 74-year-old woman with dyspnea secondary to emphysema and a 65-year-old woman with recurrent lung cancer and severe exertional fatigue and dyspnea, illustrate how dyspneic patients approaching the end of life can be evaluated and treated. Four management strategies for dyspnea are discussed: reducing ventilatory impedance, reducing ventilatory demand, improving respiratory muscle function, and altering central perception. Physicians should encourage end-stage lung disease patients and their families to discuss issues such as hospitalization and mechanical ventilation, to prepare advance directives, and to participate in a plan to manage their dyspnea.

Patient-Physician Communication During Outpatient Palliative Treatment Visits: an Observational Study—Detmar SB, Muller MJ, Wever LD, Schornagel JH, Aaronson NK. JAMA 2001 Mar 14;285(10): 1351-1357.

CONTEXT: Improving health-related quality of life (HRQL) is an important goal of palliative treatment, but little is known about actual patient-physician communication regarding HRQL topics during palliative treatment. OBJECTIVES: To investigate the content of routine communication regarding 4 specific HRQL issues between oncologists and their patients and to identify patient-, physician-, and visit-specific factors significantly associated with discussion of such issues. DESIGN: Observational study conducted between June 1996 and January 1998. SETTING: Outpatient palliative chemotherapy clinic of a cancer hospital in the Netherlands. PARTICIPANTS: Ten oncologists and 240 of their patients (72% female; mean age, 55 years) who had incurable cancer and were receiving outpatient palliative chemotherapy. MAIN OUTCOME MEASURES: Patient and physician questionnaires and audiotape analysis of communication regarding daily activities, emotional functioning, pain, and fatigue during an outpatient consultation using the Roter Interaction Analysis System. RESULTS: Physicians devoted 64% of their conversation to medical/technical issues and 23% to HRQL issues. Patients' communication behavior was divided more equally between medical/technical issues (41%) and HRQL topics (48%). Of the independent variables investigated, patients' self-reported HRQL was the most powerful predictor of discussing HRQL issues. Nevertheless, in 20% to 54% of the consultations in which patients were experiencing serious HRQL problems, no time was devoted to discussion of those problems. In particular, these patients' emotional functioning and fatigue were unaddressed 54% and 48% of the time, respectively. Discussion of HRQL issues was not more frequent in consultations in which tumor response was evaluated. CONCLUSION: Despite increasing recognition of the importance of maintaining patients' HRQL as a goal of palliative treatment, the amount of patient-physician communication devoted to such issues remains limited and appears to make only a modest contribution, at least in an explicit sense, to the evaluation of treatment efficacy in daily clinical practice.

Paradoxical Motion of the Hemidiaphragm in Patients with Emphysema—Iwasawa T, Yoshiike Y, Saito K, Kagei S, Gotoh T, Matsubara S. J Thorac Imaging 2000 Jul;15(3):191-195.

The authors evaluate paradoxical diaphragmatic motion using magnetic resonance (MR) imaging in patients with emphysema. The subjects were 12 healthy volunteers and 10 male patients with moderate to severe air flow obstruction. With subjects in the supine position, 30 sequential sagittal images of the bilateral lungs were obtained during quiet and forced breathing using a 1.5T MR unit with a body coil. The sequence

www.listening2you.com/usa

"I don't want to be playing hide and seek when I'm looking for *vital* settings."

©2000 Siemens Medical Systems, Inc., Electromedical Systems Division, 16 Electronics Avenue, Danvers, MA 01923

SIEMENS

Information is being provided for planning purposes. The ventilation system is currently under review and is not commercially available in the U.S.

Circle 131 on product info card

was single shot fast spin echo (SSFSE) with half Fourier transformation. Subtraction images were made from the original images (by subtracting a given image from the preceding image), which visualized the chest wall motion as white or black bands on the edge of the lung fields. The authors evaluated both the original and subtraction images. MR imaging showed abnormal hemidiaphragmatic motion during forced breathing: the ventral portion of the hemidiaphragm moved downward while the dorsal part moved upward like a seesaw in 6 patients. MR images also revealed abnormal ribcage motion; the ventral ribcage moved anteriorly when the hemidiaphragm moved upward in 7 patients. No abnormal motion was observed in healthy volunteers. MR is a noninvasive and useful tool for evaluating the asynchronous respiratory motion in patients with emphysema.

Systemic to Pulmonary Venous Shunt in Superior Vena Cava Occlusion—Cihangiroglu M, MacEneaney P, MacMahon H, Daehman A. J Thorac Imaging 2000 Jul;15(3):208-210.

This report describes systemic-to-pulmonary venous connections at the pleural level resulting from superior vena cava occlusion. The interval development of new venous collaterals within a 3-year period represents an advanced manifestation of SVC occlusion in this patient with a history of pleural disease. In this case, progressive venous thrombosis caused by underlying hypercoaguability led to the development of collaterals in unusual sites, including systemic-to-pulmonary venous shunting, and resulting in progressive cyanosis and death.

Alpha$_1$-Antitrypsin Deficiency: Incidence and Detection Program—Campbell EJ. Respir Med 2000 Aug;94 Suppl C:S18-S21.

Most individuals with AAT deficiency have escaped detection by healthcare systems worldwide. The large number of undiagnosed individuals has made it difficult to define the natural history of the clinical disease accurately, and severe ascertainment bias has colored the clinical descriptions of the disease. Most importantly, undetected individuals lose opportunities for important lifestyle changes and preventive therapies. To address this problem, the World Health Organization has recommended that all patients with chronic obstructive lung disease, and all adults and adolescents with asthma, be tested for AAT deficiency. Historically, the AAT Deficiency Detection Center has tested more than 30 000 individuals for the disease, and we have identified more than 1000 cases of AAT deficiency (approximately 30% of the known cases in the United States). Currently, we are implementing methods for determining AAT concentration (level), phenotype, and genotype in specimens of whole blood dried onto filter paper. This full spectrum of robust tests is performed on samples that are easily obtained and shipped to a central laboratory for processing. Wide application of these procedures may help to bring large numbers of presently undiagnosed patients to medical attention.

Marked Tachypnea in Siblings with Chronic Beryllium Disease due to Copper-Beryllium Alloy—Tarlo SM, Rhee K, Powell E, Amer E, Newman L, Liss G, Jones N. Chest 2001 Feb;119(2):647-650.

Two biological sisters working at the same factory for > 9 years developed chronic beryllium disease (CBD) from a copper-beryllium alloy. Both had marked tachypnea (36 breaths/min and 45 breaths/min at rest, respectively), persisting over 8 years. Ventilation during exercise (assessed in one sibling) was grossly excessive (57 L/min, expected 23 L/min) with a respiratory rate of 64 breaths/min even with normal baseline routine pulmonary function tests. Blood beryllium lymphocyte transformation test and lung biopsies confirmed the diagnosis. No other cases of CBD have been reported from this plant among about 120 workers. These cases support the genetic basis for berylliosis and illustrate the marked tachypnea that may accompany this disease.

Transmission of Mycobacterium Tuberculosis to a Funeral Director During Routine Embalming—Lauzardo M, Lee P, Duncan H, Hale Y. Chest 2001 Feb;119(2):640-2.

Several studies have shown that funeral directors have an increased risk of tuberculosis (TB). Although there is indirect evidence of transmission of TB from cadavers to mortuary workers, there is only one recently documented case in the literature. We report here another case of occupationally acquired TB in a funeral director, which was confirmed by conventional epidemiology and genotyping. This case illustrates the risk of TB transmission to mortuary workers from routine embalming of deceased TB patients with active disease.

Diaphragmatic Paralysis Following Cervical Chiropractic Manipulation: Case Report and Review—Schram DJ, Vosik W, Cantral D. Chest 2001 Feb;119(2):638-640.

This case report documents an uncommon cause of bilateral diaphragmatic paralysis resulting from phrenic nerve injury during cervical chiropractic manipulation. Several months after the initial injury, our patient remains short of breath and has difficulty breathing in the supine position. Other causes of diaphragmatic paralysis and phrenic nerve injury are reviewed.

Gene Therapy for Pulmonary Diseases—West J, Rodman DM. Chest 2001 Feb;119(2):613-617.

Gene therapy for pulmonary disease has attracted a great deal of attention since the first report of successful gene delivery 10 years ago. Potential indications for gene therapy include chronic illnesses such as cystic fibrosis and alpha$_1$-antitrypsin deficiency, and acute illnesses such as acute transplant rejection and chemotherapy-induced lung injury. The key technological impediment to successful gene therapy is vector optimization. Viral vectors, including adenovirus and adeno-associated virus, have relatively low efficiency in vivo. In addition, adenovirus has been associated with a brisk inflammatory response and limited duration of expression in the lung. Nonviral vectors, particularly liposomes, have also been tried, with limited expression efficiency and some toxicity. Although work is ongoing to improve adenoviral and adeno-associated viral vectors and test other viral and nonviral vectors, an ideal vector has not yet been identified. Several important barriers to successful gene therapy, including the host inflammatory response, promotor down-regulation, tissue-specific targeting, and physical barriers to gene delivery in the airway, will need to be overcome. Despite these daunting problems, several human gene therapy trials have been completed, using adenovirus, adeno-associated virus, and liposomes. In general, these trials have been focused on safety, and have shown that there is dose-dependent inflammation in response to adenovirus. Adeno-associated virus appears to cause little inflammation. Demonstration of successful gene delivery and transcription has been quite variable in human trials. In general, the level of expression of transgene appears to be quite low. In summary, although there is great promise for gene therapy in the lung, significant challenges remain in translating this technology to successful human therapy.

Do Surrogate Decision Makers Provide Accurate Consent for Intensive Care Research?—Coppolino M, Ackerson L. Chest 2001 Feb; 119(2):603-612.

CONTEXT: ICU patients are often rendered incapable of making decisions as a result of their illness. The accuracy with which patients' surrogates consent to research on their behalf is not known. OBJECTIVE: To determine if surrogate decision makers provide accurate consent for intensive care research. DESIGN: Cross-sectional, paired, face-to-face interviews. SETTING: A large, managed-care, cardiac surgery

service. PATIENTS AND PATICIPANTS: One hundred elective cardiac surgery patients and their self appointed surrogates were enrolled. INTERVENTION: Patients agreed or declined to provide informed consent to two hypothetical research trials. One trial represented minimal risk to those enrolled, the other trial represented greater-than minimal risk. Surrogates attempted to predict the patients' responses. Main outcome measures: The accuracy of surrogate consent was analyzed in a fashion analogous to the evaluation of a diagnostic test. Predictors of accuracy were evaluated using multiple logistic regression. RESULTS: Overall surrogate positive predictive value for the low-risk study was 84.0% and for the high-risk study was 79.7% ($p = 0.72$, McNemar test). Predictors of accurate consent were not consistent across the two studies. CONCLUSIONS: Surrogate decision makers for critical-care research resulted in false-positive consent rates of 16 to 20.3%. Further assessment and evaluation of the practice of surrogate consent for intensive care research is, therefore, recommended.

The Costs of Treating COPD in the United States—Strassels SA, Smith DH, Sullivan SD, Mahajan PS. Chest 2001 Feb;119(2):344-352.

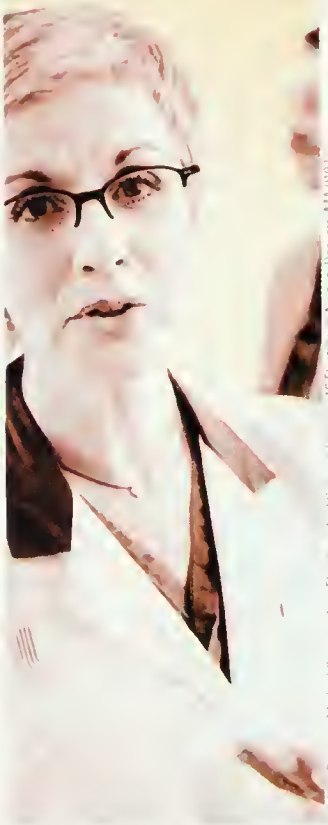
STUDY OBJECTIVES: COPD affects millions of people in the United States. The purpose of this study was to describe the medical resource use and costs incurred by persons with COPD in the United States in 1987. DESIGN: Data for this study were derived from the 1987 National Medical Expenditure Survey. A societal perspective was adopted for this analysis. PATIENTS OR PARTICIPANTS: All persons ≥ 40 years old with resource use or expenditures for chronic bronchitis, emphysema, or nonspecific chronic airway obstruction were included in this study. RESULTS: Mean per-person direct medical expenditures among persons with COPD were $6,469 (1987 US dollars), about 25% of which was COPD related. Approximately 68% of direct medical expenditures in persons with COPD were for inpatient hospitalization. CONCLUSIONS: COPD causes a large societal burden of illness that is expected to increase. This study provides a valuable foundation and historical measure against which to compare other estimates.

Nutritional Intervention in COPD: A Systematic Overview—Ferreira I, Brooks D, Lacasse Y, Goldstein R. Chest 2001 Feb;119(2):353-363.

OBJECTIVE: We conducted a systematic overview of randomized controlled trials (RCTs) to clarify the contribution of nutritional supplementation for patients with stable COPD. METHODS: RCTs were identified from several sources, including the Cochrane Airways Group register of RCTs, a hand search of abstracts presented at international meetings, and consultation with experts. Two reviewers independently selected trials for inclusion, assessed quality, and extracted the data. RESULTS: Twenty-one reports were classified according to the type, duration of supplementation, and the presence of anabolic substances. High carbohydrate meals were associated with an increase in carbon dioxide production and a decrease in exercise capacity. Short-term crossover studies in which diets of various compositions were administered supported the notion that high carbohydrate loads increase the stress on the ventilatory system. The influence of longer-term supplementation (> 2 weeks) on weight, anthropometry, and exercise capacity varied, without there being a consistent effect. Lean body weight was only occasionally reported and health-related quality of life too rarely to be included as an outcome. The influence of recombinant human growth hormone was disappointing. Anabolic steroids increased body weight and lean body mass, but had little influence on exercise capacity. CONCLUSION: This systematic overview in patients with COPD supports the notion that those with marginal ventilatory reserve might benefit from a dietary regimen in which a high percentage of calories are supplied by fat. Although there are reports of the benefits of nutritional repletion, trials of > 2 weeks failed to show consistent benefit on body weight. Evaluating nutritional repletion is hampered by the absence of information regarding body

www.listening2you.com/usa

"Why can't I have a ventilation platform with the clinical performance to treat all patient categories?"



SIEMENS

Information is being provided for planning purposes. The ventilation system is currently under review and is not commercially available in the U.S.

Circle 132 on product info card

composition, exercise, and health-related quality of life. Growth hormone has not been shown to be useful. Further studies are needed to refine the beneficial effects of anabolic steroids as adjunctive agents together with nutritional support and exercise.

Impact of a Hospital-Based Home-Care Program on the Management of COPD Patients Receiving Long-Term Oxygen Therapy—Farrero E, Escarrabill J, Prats E, Maderal M, Manresa F. Chest 2001 Feb;119(2):364-369.

STUDY OBJECTIVES: To analyze the influence of a hospital-based home-care program (HCP) on the management of patients with COPD receiving long-term oxygen therapy. DESIGN AND SETTING: Randomized, controlled study in a 1,000-bed university hospital. INTERVENTION: The HCP applied to patients in the intervention group (HCP group) consisted of a monthly telephone call, home visits every 3 months, and home or hospital visits on a demand basis. Patients in the control group were given conventional medical care. MEASUREMENTS: Pulmonary function data, gas exchange, use of hospital resources (emergency department visits, admissions, and hospital stay) and the cost of medical assistance were investigated in both groups before and after 1 year of study. Quality of life was analyzed using the chronic respiratory questionnaire in the first 40 consecutive patients included in the study. Survival throughout the study was also assessed. RESULTS: One hundred twenty-two patients were enrolled in the study, and 94 patients (46 in the HCP group and 48 in the control group) completed the 1-year follow-up period; 83 patients (88%) were men, and mean (± SD) age was 68 ± 8 years. During the follow-up period, there was a highly significant decrease in the mean number of emergency department visits (0.45 ± 0.83 vs 1.58 ± 1.96; p = 0.0001) and also a significant decrease in hospital admissions (0.5 ± 0.86 vs 1.29 ± 1.7; p = 0.001) and days of hospital stay (7.43 ± 15.6 vs 18.2 ± 24.5; p = 0.01) in the HCP group. Patients in the intervention group required a total of 221 home visits (mean per patient, 4.8 ± 0.8) and 69 hospital visits (mean per patient, 1.5 ± 1.07). In spite of the cost of the program, cost analysis showed a total saving of 8.1 million pesetas ($46,823) in the HCP group, mainly due to a decrease in the use of hospital resources. There was no difference in pulmonary function, gas exchange, quality of life, and survival between the two groups. CONCLUSIONS: Hospital-based home care is an effective alternative to hospital admission. It reduces the use of hospital resources and the cost of health care.

Regular Inhaled Salbutamol: Effect On Airway Responsiveness to Methacholine and Adenosine 5'-Monophosphate and Tolerance to Bronchoprotection—Jokic R, Swystun VA, Davis BE, Cockcroft DW. Chest 2001 Feb;119(2):370-375.

OBJECTIVE: Regular treatment with inhaled $beta_2$-agonists increases airway responsiveness consistently to indirect bronchoconstrictors (allergen, exercise, hypertonic saline solution, etc) and inconsistently to direct bronchoconstrictors (histamine, methacholine). Studies demonstrating tolerance to $beta_2$-agonist bronchoprotection against the indirect bronchoconstrictor adenosine 5'-monophosphate (AMP) have not examined changes in baseline AMP responsiveness. This study assessed the effect of regular salbutamol on AMP and methacholine responsiveness and on tolerance to bronchoprotection. DESIGN: Double-blind, randomized, crossover study. SETTING: University hospital bronchoprovocation laboratory. PATIENTS: Fourteen atopic asthmatic subjects with FEV_1 > 65% predicted, and methacholine provocative concentration causing a 20% fall in FEV_1 (PC_{20}) < 8 mg/mL. INTERVENTIONS: Salbutamol, 100 microg, and placebo inhalers, two puffs qid, each for 10 days. MEASUREMENTS: Methacholine PC_{20} and AMP PC_{20} measured 12 h after blinded inhaler after each treatment period. Methacholine PC_{20} and AMP PC_{20} repeated 10 min after salbutamol, 200 microg (eight subjects). RESULTS: There was no difference between placebo and salbutamol treatment in geometric mean methacholine PC_{20} (0.85 mg/mL vs 0.82 mg/mL, p = 0.86) or AMP PC_{20} (22 mg/mL vs 17.4 mg/mL, p = 0.21; n = 14). The acute bronchoprotective effect of salbutamol was greater vs AMP than vs methacholine (5.1 doubling concentrations vs. 3.5 doubling concentrations, p = 0.06) and loss of protective effect of salbutamol (mean ± SD) was greater vs AMP than vs. methacholine (2.4 ± 0.33 doubling concentration loss vs 0.8 ± 0.21 doubling concentration loss, p = 0.008; n = 8). CONCLUSION: Regular salbutamol (mean ± SD) treatment did not enhance airway responsiveness to either the indirect bronchoconstrictor AMP or the direct bronchoconstrictor methacholine. Compared to its effect on methacholine, salbutamol had a greater acute protective effect vs AMP and produced greater loss of protection vs AMP when used regularly.

Thoracic Dimensions at Maximum Lung Inflation in Normal Subjects and in Patients with Obstructive and Restrictive Lung Diseases—Bellemare JF, Cordeau MP, Leblanc P, Bellemare F. Chest 2001 Feb;119(2):376-386.

OBJECTIVES: To compare the distribution of lung volume at total lung capacity (TLC) among adult men and women known to have normal lung function or chronic obstructive disease or restrictive lung disease (RLD). DESIGN: Five-year retrospective study. SETTING: Review of available clinical pulmonary function testing (PFT) reports and chest radiographs. PATIENTS: Sixty-four patients presenting with normal PFT and chest radiograph findings (normal subjects), 26 patients with severe COPD and increased TLC (COPD group), 29 patients with cystic fibrosis (CF) and increased TLC (CF group), and 19 patients with RLD with a clinical diagnosis of pulmonary fibrosis and a reduced TLC (RLD group). MEASUREMENTS: Average posteroanterior rib cage diameter (PA_{ave}), average lateral rib cage diameter (LA_{ave}), and average vertical height of the diaphragm (HDI_{ave}) were measured using radiography. Normal prediction equations were generated based on stature, body mass index (BMI), age, and sex as independent variables and then used in between-group comparisons. RESULTS: PA_{ave} correlated positively with BMI and age but not with height, whereas LA_{ave} correlated positively with BMI and height but not with age. HDI_{ave} correlated positively with height and age but negatively with BMI. PA_{ave} and LA_{ave} were smaller and HDI_{ave} was greater in women than men having the same stature. In the COPD group and in male CF group patients, BMI was low and only HDI_{ave} was greater than in sex-, age-, and height-matched normal subjects, but in female CF group patients, only the rib cage diameters were greater than normal. In the RLD group, PA_{ave} and HDI_{ave} were smaller than predicted and inversely related to each other, but LA_{ave} was normal. CONCLUSION: Variations in maximum lung volume caused by gender, growth, or by lung diseases are nonisotropic and entail substantial changes in chest wall shape.

Effects of Levodopa on Pulmonary Function in Parkinson's Disease—Herer B, Arnulf I, Housset B. Chest 2001 Feb;119(2):387-393.

STUDY OBJECTIVES: Upper-airway obstruction (UAO) may be present in patients with Parkinson's disease (PD), and its reversibility after levodopa therapy has been suggested. To investigate the effects of oral intake of levodopa on pulmonary function and UAO criteria in patients with PD, we studied 22 patients with PD. DESIGN: Pulmonary function tests were performed after a 12-h withdrawal of levodopa therapy, and 1 h after oral intake of placebo or levodopa, according to a double-blind, placebo-controlled, crossover study. Six UAO criteria were recorded to detect UAO in patients. UAO was found in 5 of 21 patients on baseline conditions (1 patient could not perform all tests). RESULTS: Among the patients with UAO, after levodopa therapy three of five patients did not meet the four of six required criteria for defining UAO. Levodopa produced its effects on UAO criteria by means of a saw-tooth pattern improvement and/or a decrease below the defined thresholds of the peak inspiratory flow and the FEV_1/peak expiratory flow (PEF) and FEV_1/

www.listening2you.com/usa

forced expiratory flow after 50% of the FVC ($FEV_{0.5}$) ratios. Levodopa PEF increased by 0.85 L/s in patients with UAO and by 0.24 L/s in patients without UAO, while after placebo it increased by 0.03 L/s in patients with UAO and decreased by 0.16 L/s in patients without UAO ($p = 0.02$). Whereas in patients without UAO an increase of the FEV_1/PEF and $FEV_1/FEV_{0.5}$ ratios was observed after placebo and levodopa intake, these ratios decreased after levodopa and increased after placebo in patients with UAO. CONCLUSIONS: These results show that levodopa administration in patients with PD induces significant variations in PEF and UAO ratios (FEV_1/PEF and $FEV_1/FEV_{0.5}$).

Performance of Nasal Prongs in Sleep Studies: Spectrum of Flow-Related Events—Hernandez L, Ballester E, Farre R, Badia JR, Lobelo R, Navajas D, Montserrat JM. Chest 2001 Feb;119(2):442-450.

OBJECTIVES: The use of nasal prongs connected to a pressure transducer is a noninvasive, sensitive method to detect respiratory events, and can be easily implemented in routine sleep studies. Moreover, its good time response allows the detection of several flow-related phenomena of high interest, in addition to apnea and hypopnea. The aims of the study were to examine the quality and performance of the nasal prong flow signal, and to describe other flow-related events during full-night polysomnography studies. METHODS: Twenty-seven subjects were studied (16 male subjects; mean ± SD age, 49 ± 14 years; mean body mass index, 27 ± 4 kg/m^2): 15 subjects recruited from the general population and 12 consecutive patients with suspected sleep apnea/hypopnea syndrome (SAHS). RESULTS: A blind analysis of the respiratory events detected both by nasal prongs and thermistor was done. The quality of the nasal prong signal recordings was considered optimal for scoring purposes in 78% of cases, and no recording was considered uninterpretable. The nasal prong signal detected additional flow-related events not observed by the thermistor: (1) short and long (> 2 min) periods of inspiratory flow limitation morphology without decrease in the amplitude of the signal; (2) periods of mouth expiration; and (3) snoring. The apnea/hypopnea index was significantly higher with the nasal prong scoring (18 vs 11 [$p < 0.05$] in the general population and 37 vs 27 [$p < 0.001$] in the group with suspected SAHS). CONCLUSIONS: The incorporation of nasal prongs in routine full-night studies is an attainable technical option that provides adequate recordings in most cases. Additionally, relevant information not scored by thermistors is obtained on flow-related respiratory events, thus increasing diagnostic accuracy.

Breath-to-Breath Variability Correlates with Apnea-Hypopnea Index in Obstructive Sleep Apnea—Kowallik P, Jacobi I, Jirmann A, Meesmann M, Schmidt M, Wirtz H. Chest 2001 Feb;119(2):451-459.

BACKGROUND: Breathing in patients with obstructive sleep apnea (OSA) is frequently interrupted by periods of hypopnea and apnea. There is limited information regarding a possible disturbance of breathing outside these periods. STUDY OBJECTIVE: To analyze the degree of breathing disturbance during nonocclusion. DESIGN: Prospective determination of breathing variability during full polysomnographic sleep studies. PATIENTS: Breath-to-breath variation was monitored in 34 patients with OSA and in 9 healthy subjects. MEASUREMENTS AND RESULTS: All breath-to-breath intervals were automatically analyzed from flow signal, displayed, and manually corrected for artifacts. Distribution of all nonapneic breath intervals was analyzed for the extent of difference from a normal distribution pattern by specifying kurtosis. In untreated OSA patients, kurtosis was significantly reduced (0.0 ± 0.5, mean ± SD) compared to control subjects (0.8 ± 0.5), indicating increased variability of nonoccluded breathing. This effect was present in all sleep stages, and the extent depended significantly on the degree of disease. Continuous positive airway pressure breathing was able to normalize kurtosis (1.0 ± 0.9) immediately. CONCLUSIONS: Breathing in OSA is not only characterized by interruptions of breathing during occlusion, but by a greater variation in the pattern of normal-length breaths.

"I'd like to be able
to mention ventilatory
treatment
performance
and cost-efficiency
in the same breath."
SIEMENS
Information is being provided for planning purposes.
The ventilation system is currently under review and
is not commercially available in the U.S.
Circle 133 on product info card

New International Guidelines for Chronic Obstructive Pulmonary Disease

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is an international project with the goals of increasing awareness of chronic obstructive pulmonary disease (COPD) and decreasing morbidity and mortality from this disease worldwide.[1] Co-sponsored by the National Heart, Lung, and Blood Institute of the United States National Institutes of Health and the World Health Organization, the GOLD project was supported financially through educational grants from 17 corporations, including the major pharmaceutical companies with interests in obstructive lung disease.

GOLD is an ambitious project that will take several years to complete. Starting this spring, its Web site (http://www.goldcopd.com) has posted several documents, among which is the Executive Summary reprinted in this issue of Respiratory Care. Other resources available at the GOLD Web site, all in the public domain, include the full GOLD Workshop Report (136 pages), a 74-slide downloadable teaching slide set covering the material in the Executive Summary, and a set of charts with instructions for using all the currently available inhalers and spacers for bronchodilator and corticosteroid therapy.

The GOLD Executive Summary first covers the diagnosis and staging of COPD and then discusses its epidemiology, economic and social burden, and risk factors. Most of the report is then devoted to 4 components of COPD management: assessment and monitoring of disease, reduction of risk factors, management of stable disease, and management of acute exacerbations. The document concludes by identifying several important areas for future research.

As the product of an international collaborative effort, GOLD contains a few elements that may be relatively new to United States clinicians, although its recommendations should be applicable to practice throughout the world. It differs in a number of respects from the primary COPD management standard used until now in North America, that of the American Thoracic Society (ATS) published in 1995.[2] Most of the differences reflect the evolution of our knowledge in various aspects of COPD, although some differences are controversial and imply changes in assessment and management with substantial potential impact on the economics of managing this disorder. I will highlight a few of the more notable features of the new guidelines.

Making the diagnosis of COPD, according to GOLD, relies on spirometry, following administration of inhaled bronchodilator, to identify incompletely reversible airflow limitation. Classification of COPD patients according to disease severity differs to a minor degree from the scheme used in the ATS Standards.[2] The ATS guidelines do not define airflow limitation in terms of a fixed ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity. According to the ATS standards, COPD patients are in Stage I when FEV_1 is $\geq 50\%$ of the predicted value, in Stage II when FEV_1 is between 35 and 49% of predicted, and in Stage III when FEV_1 is $< 35\%$ of predicted. The ATS staging system is based solely on airflow limitation, with hypoxemia and right heart failure considered separately, while the new GOLD system (Table 1) incorporates all 3 of these elements.

In the GOLD system, even patients with moderate airflow limitation are classified as Stage III if they have hypoxemia or signs of right heart failure. Arterial partial pressure of carbon dioxide is not used in staging.

GOLD is appearing in an era of evidence-based medicine and specifies the strength of the evidence supporting many of its recommendations. Table 2 summarizes the areas in COPD management in which the GOLD authors classify the available evidence as at the highest level.

New since release of the ATS standards is the recommendation for use of combinations of bronchodilators from different classes, such as albuterol plus ipratropium or theophylline.[1] The long-acting β-agonist inhaled bronchodilator salmeterol had just been introduced in the United States when the ATS standards were published: as GOLD appears it is being joined in this country by formoterol, another long-acting agent. GOLD has incorporated long-acting β agonists into its management recommendations for stable patients, citing level "B" evidence from a study showing improved health status in COPD patients treated regularly with salmeterol.[3]

The biggest change in the new recommendations relates to the use of corticosteroids. For acute exacerbations, GOLD recommends short-term administration of prednisone or other (preferably oral) systemic corticosteroid as primary therapy. While this recommendation is consistent with the practice of most clinicians, the stance taken toward corticosteroid use in clinically stable patients fuels an already

Table 1. Classification of COPD by Severity

Stage 0: At Risk	Symptoms Normal FEV_1 and FEV_1/FVC
Stage I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ of predicted
Stage II: Moderate COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 80\%$ of predicted
Stage IIA:	FEV_1 50–79% of predicted
Stage IIB:	FEV_1 30–49% of predicted
Stage III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ of predicted *or* $P_{aO_2} < 60$ mm Hg *or* Clinical signs of right heart failure

COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
P_{aO_2} = arterial partial pressure of oxygen

established controversy.[4,5] The ATS standards state that perhaps 20–30% of stable patients improve with long-term oral corticosteroid therapy but caution that this should not be undertaken unless objective (presumably spirometric) improvement has been documented.[2] The new guidelines advise against long-term use of oral corticosteroids in COPD patients, citing level "A" evidence that such use is unacceptably hazardous.[1]

The ATS standards do not recommend the use of inhaled corticosteroids in non-asthmatic COPD patients, stating that "Adding an inhaled steroid to a regimen that includes regular aerosol therapy with ipratropium and a β agonist results in the probability of noncompliance being increased."[2] However, the new GOLD guidelines recommend inhaled corticosteroid therapy for many COPD patients: those with a 15% increase in FEV_1 (at least 200 mL) with 6–12 weeks of inhaled corticosteroid therapy, and those with FEV_1 <50% of predicted and frequent acute exacerbations. What is meant by "frequent" acute exacerbations is not specified. GOLD discounts previous studies suggesting that steroid-responsive patients can be identified using a short therapeutic trial of prednisone and cites evidence that such a trial is a poor predictor of the long-term response to inhaled corticosteroids.[6,7]

The recommendation that inhaled corticosteroids be widely used in treating COPD patients is based mainly on the results of the ISOLDE (Inhaled Steroids in Obstructive Lung Disease) study, a large-scale European study comparing inhaled fluticasone (500 μg twice daily) to placebo in patients with moderate to severe COPD.[6] Like 3 other recently-published multicenter clinical trials in patients with less severe COPD,[8–10] the ISOLDE study found that inhaled corticosteroid use did not affect the decline of lung function.[6] However, ISOLDE documented that the frequency of acute exacerbations was reduced and that quality of life, as assessed by the St George's Respiratory Questionnaire,[11] declined less rapidly in the inhaled steroid-treated patients. Specifically, acute exacerbations (defined as episodes for which the patients' primary physicians prescribed a course of antibiotics or oral corticosteroids) were 0.99/yr in the fluticasone group, versus 1.32/yr in the placebo group, a reduction of 25% ($p = 0.026$).[6]

In the ISOLDE study, the patients' mean decline in health status during the 36 months of the study (mainly because of the difference in acute exacerbations) was from a score of 48 to a score of 53 units on the St George's Respiratory Questionnaire in the fluticasone-treated pa-

Table 2. Elements of COPD Management that are Supported by Level "A" Evidence*

Management of Stable COPD
Smoking cessation (all patients)
General (both effective and cost-effective)
Brief tobacco dependence treatment
Practical counseling
Social support as part of treatment
Social support arranged outside of treatment
Nicotine replacement therapy
Adjunctive agents (bupropion, nortriptyline)
Health education (all patients)
Self-management skills
Coping ability
Health status
Bronchodilators (for symptom management)
β agonists
Anticholinergics
Theophylline
Combinations
Exercise training programs (all stages of disease)
Exercise tolerance
Dyspnea
Fatigue
Long-term oxygen therapy (increases survival in selected patients)
Management of acute exacerbations
Bronchodilator therapy (all patients)
Inhaled bronchodilators (short-acting β agonists, anticholinergics)
Theophylline
Systemic corticosteroids (all patients)
Noninvasive positive pressure ventilation (hospitalized patients)
Improved arterial blood gases
Decreased need for intubation and invasive mechanical ventilation
Decreased in-hospital mortality
Decreased hospital length of stay

COPD = chronic obstructive pulmonary disease
*Level "A" evidence: Consistent evidence, in large numbers of patients, from randomized controlled trials using relevant end points in the target patient population. (Adapted from Reference 1.)

tients (higher scores mean worse health status), as compared to changes in mean scores from 50 to 56 units in the placebo-treated patients.[6] A change in total score of 4 or more units represents a clinically important change in the patient's condition.[12] Thus, at the reported rate of decline, patients receiving fluticasone would be expected to reach a clinically detectable change in health status on average 9 months later than patients receiving placebo (after 24 vs 15 months of therapy). Although statistically significant, the clinical relevance of these differences has been called into question.[5]

The long-term safety of inhaled corticosteroids is still unclear, particularly in middle-aged and elderly individuals and at the high doses used in the ISOLDE[6] and Lung Health studies.[10] The Lung Health study, which used triamcinolone, found statistically significant decreases in bone density (both lumbar spine and femur) during the 40-month study in the inhaled corticosteroid-treated patients, as compared to patients on placebo.[10]

Another meaning of the word "gold" can be applied to the new guidelines when it comes to inhaled corticosteroids, as the cost implications of the recommendations are staggering. As of June 1, 2001, at the outpatient pharmacy of the hospital at which I practice, the cost to the patient of fluticasone, two 220 μg puffs via metered-dose inhaler twice daily (which is 12% less than the dose used in the ISOLDE study) is $87.95 per month, or approximately $1,000 per year. A main outcome benefit from the ISOLDE study, on which the GOLD recommendations are based, was a mean decrease of 0.33 acute exacerbations per patient-year, as compared to placebo.[6] This means that, if an average patient from that study were being managed at my hospital, it would take 3 years and $3,000 worth of fluticasone to prevent one acute exacerbation requiring treatment with prednisone or antibiotics.

This is not to disparage the design or reporting of the ISOLDE study, nor the recommendations of the GOLD Scientific Committee, but to call attention to the costs involved and the relative magnitude of the benefits that may be realized by widespread use of inhaled corticosteroids in COPD patients. The horse is already out of the barn, of course, because inhaled corticosteroids are already widely prescribed for COPD in the United States—to the tune of millions of prescriptions annually. However one interprets the results of the ISOLDE study and other available data on inhaled corticosteroids in COPD, cost considerations highlight the importance of smoking cessation and other interventions in the huge number of early COPD cases, in order to prevent or delay progression to stages in which quality of life declines sharply and medication costs rise, with less potential gain from therapy.

The GOLD Workshop Report mentions advance directives and end-of-life planning[13] only in passing, and it does not discuss the terminal management of COPD patients. In fact, the guidelines state that narcotics are contraindicated in patients with COPD, because of their respiratory depressant effects, without mentioning the important role narcotics play in the palliation of dyspnea for the patient dying of COPD.[14] Palliative care is assuming an increasing role in the management of patients with chronic respiratory disease,[15] and one can only hope that guidance for clinicians in this important area of COPD management is added in the future.

These issues notwithstanding, the new guidelines are clinically relevant, practical, and clearly written. Because of the enormous burden of COPD in our society and its increasing importance in our aging population, the GOLD Executive Summary and its associated documents and teaching materials are important documents for clinicians. Their dissemination and implementation should benefit our patients, facilitate teaching, and stimulate much needed additional research in the care of COPD.

David J Pierson MD FAARC
Editor in Chief, Respiratory Care
Division of Pulmonary and Critical Care Medicine
Department of Medicine
Harborview Medical Center
University of Washington
Seattle, Washington

REFERENCES

1. Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS, on behalf of the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Executive Summary. Respir Care 2001;46(8):798–825.
2. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152(5 Pt 2):S77–S121.
3. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med 1997;155(4): 1283–1289.
4. Calverley PM. Inhaled corticosteroids are beneficial in chronic obstructive pulmonary disease (editorial). Am J Respir Crit Care Med 2000;161(2 Pt 1):341–342; discussion, 344
5. Barnes PJ. Inhaled corticosteroids are not beneficial in chronic obstructive pulmonary disease (editorial). Am J Respir Crit Care Med 2000;161(2 Pt 1):342–344; discussion, 344.
6. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320(7245):1297–1303.
7. Senderovitz T, Vestbo J, Frandsen J, Maltbaek N, Norgaard M, Nielsen C, Kampmann JP. Steroid reversibility test followed by inhaled budesonide or placebo in outpatients with stable chronic obstructive pulmonary disease. The Danish Society of Respiratory Medicine. Respir Med 1999;93(10):715–718.
8. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic

obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353(9167):1819–1823.

9. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999;340(25): 1948–1953.
10. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343(26):1902–1909.
11. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145(6): 1321–1327.
12. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991;85(Suppl B):25–31; discussion 33–37.
13. Curtis JR. Communicating with patients and their families about advance care planning and end-of-life care. Respir Care 2000;45(11): 1385–1394, discussion 1394–1398.
14. Luce JM, Luce JA. Perspectives on care at the close of life. Management of dyspnea in patients with far-advanced lung disease: "Once I lose it, it's kind of hard to catch it ...." JAMA. 2001;285(10):1331–1337.
15. State-of-the-Art Conference on Palliative Respiratory Care. Respir Care 2000;45(11,12):1318–1410, 1460–1540.

Correspondence: David J Pierson MD FAARC, Respiratory Care Editorial Office, 600 Ninth Avenue, Suite 702, Seattle WA 98104. E-mail: pierson@aarc.org.

Weaning Children from Mechanical Ventilation: A Prospective Randomized Trial of Protocol-Directed Versus Physician-Directed Weaning

Theresa Ryan Schultz RN RRT, Richard J Lin MD, H Marc Watzman MD, Suzanne M Durning RRT, Roberta Hales RRT, Arnetta Woodson RN, Barbara Francis RRT, Lisa Tyler RRT, Linda Napoli RRT RPFT, and Rodolfo I Godinez MD PhD

OBJECTIVE: Compare outcomes between physician-directed and protocol-directed weaning from mechanical ventilation in pediatric patients. DESIGN: Prospective-randomized. SETTING: Pediatric and cardiac intensive care units in a 307-bed tertiary referral hospital for children. INTERVENTIONS: The control group (physician-directed) was weaned according to individual physician order for reduction in minute ventilation, positive end-expiratory pressure, and ordered oxygen saturation parameters for reduction in fraction of inspired oxygen (F_{IO_2}). The study group (protocol-directed) was weaned according to a predetermined algorithm developed for the purpose of this investigation. METHODS: The study enrolled 223 patients (116 physician-directed, 107 protocol-directed). All patients were monitored for hemodynamics, ventilator parameters, arterial blood gas values when available, oxygen saturation, weaning time, pre-weaning time, extubation time, and time on $F_{IO_2} \geq 0.40$. We also monitored the incidence of reintubation, subglottic stenosis, tracheitis, and pneumonia. The protocol-directed group had additional measurements of actual versus predicted minute volume, comparisons of respiratory rate (actual versus predicted for age), and presence of spontaneous breathing effort for 10 consecutive minutes. Data analysis was done according to intent to treat. RESULTS: There was no significant difference in 12-hour and 24-hour pediatric risk of mortality (PRISM III) scores between groups. The protocol-directed group overall had shorter total ventilation time, weaning time, pre-weaning time, time to extubation, and time on $F_{IO_2} > 0.40$, although after stratification for respiratory diagnosis, only the difference in weaning time remained significant. There was no difference in the incidence of reintubation, new-onset tracheitis, subglottic stenosis, or pneumonia. CONCLUSIONS: Protocol-directed weaning resulted in a shorter weaning time than physician-directed weaning in these pediatric patients. *Key words: mechanical ventilation, pressure support, synchronized intermittent mandatory ventilation, SIMV, minute ventilation, protocol-directed weaning, physician-directed weaning, pediatric mechanical ventilation.* [Respir Care 2001;46(8):772–782]

Introduction

The need to efficiently care for patients in an environment in which supply and demand for health care services are ever-changing has inspired the implementation of protocols. Mechanical ventilation is a high-volume process in intensive care and thus can be efficiently conducted by protocol. Mechanical ventilation can be a critical component in postoperative care as well as in the management of respiratory, circulatory, metabolic, and neurologic failure. Weaning from mechanical ventilation is the transition to self-sufficient respiratory function during recovery, and can account for as much as 40% of the time that a patient receives mechanical ventilation.[1] Traditionally, this process has required physicians to use weaning strategies and to be physically present to closely monitor how the patient

Theresa Ryan Schultz RN RRT, Richard J Lin MD, Suzanne M Durning RRT, Roberta Hales RRT, Arnetta Woodson RN, Barbara Francis RRT, Linda Napoli RRT RPFT, and Rodolfo I Godinez MD PhD are affiliated with The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. H Marc Watzman MD was affiliated with The Children's Hospital of Philadelphia at the time of this study, but is now with the Department of Anesthesia and Critical Care, The Pritzker School of Medicine, University of Chicago, Chicago, Illinois.

Preliminary versions of this paper were presented by Theresa Ryan Schultz RN RRT at the 45th International Respiratory Congress of the American Association for Respiratory Care, December 13–16, 1999, Las Vegas, Nevada, and by H Marc Watzman MD at the annual meeting of the Society for Critical Care Medicine, February 12, 2000, Orlando, Florida.

Correspondence: Theresa Ryan Schultz RN RRT, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia PA 19104-4399. E-mail: schultz@email.chop.edu.

tolerates the reduction of ventilatory support. However, several inefficiencies exist in that system.

Recovery of respiratory function, either from resolution of post-anesthetic effect or from treatment of organ system failure, is often not predictable. Physicians may not be available to begin weaning ventilatory support when the patient is ready. Also, the weaning process is frequently based on subjective assessments of how a patient is tolerating decreases in mechanical ventilation, rather than on objective assessments.

Delay in weaning from mechanical ventilation may lead to unnecessary discomfort for the intubated patient, increased costs associated with unnecessary resource use, and increased risk of complications related to intubation and mechanical ventilation. These risks can include airway complications such as vocal cord paralysis, subglottic stenosis, and tracheitis; and parenchymal complications such as ventilator-associated pneumonia, ventilator-induced lung injury, and pneumothoraces. Patients requiring prolonged mechanical ventilation have a lower survival rate. Kollef et al suggest that reducing the duration of ventilatory support may improve patient outcomes, possibly by reducing the occurrence of nosocomial infections and systemic complications.[2]

Weaning patients from mechanical ventilation involves decreasing the level of ventilatory support and challenging the patient's work of breathing. Weaning modes commonly used include synchronized intermittent mandatory ventilation (SIMV), pressure-support ventilation (PSV), continuous positive airway pressure, and T-piece.[3,4] Though most mechanical ventilation techniques use intermittent mandatory ventilation, specific weaning strategies are usually derived from clinician preferences rather than scientifically proven methodologies.[5]

Recent investigations have compared outcomes of physician-directed weaning with those of protocol-directed weaning programs. In several large studies involving adult intensive care unit (ICU) patients receiving mechanical ventilation, protocol-directed weaning was shown to be superior to physician-directed weaning in the reduction of total mechanical ventilation time and shorter total hospital costs per patient.[3,6–8] Some studies have shown shorter mechanical ventilation time and total hospital time in patients receiving protocol-directed weaning using PSV than in those receiving either physician-directed weaning or protocol-directed weaning with other mechanical ventilation modalities.[7,9] However, none of those studies included pediatric patients.

The purpose of our study was to compare the outcomes of traditional physician-directed weaning versus a protocol-directed strategy in pediatric patients. Our protocol uses PSV weaning, since the literature suggests its superiority over other weaning modes.[10–13] For purposes of standardization, we also developed weaning end points that are similar to extubation criteria in accepted ICU practice and weaning parameters supported in the literature.[14]

Methods

A prospective, randomized, controlled study was approved by the institutional review board at The Children's Hospital of Philadelphia. Patients were enrolled from our 38-bed pediatric intensive care unit (PICU) and 20-bed cardiac intensive care unit (CICU) over a 2-year period. Documentation of verbal informed consent was obtained from each child's parent/guardian on enrollment. All admitted patients who required intubation and mechanical ventilation were eligible for the study. Patients were excluded if they had central apnea, required chronic mechanical ventilation, or met criteria for brain death. ICU therapists identified and enrolled patients Monday through Friday only, even though weaning of enrolled patients could begin at any time.

Patients were assigned by computer-generated randomization to either a control group, which received physician-directed (PHY) weaning, or a study group, which received protocol-directed (PRO) weaning. The enrollment and randomization occurred at the onset of mechanical ventilation or on admission to our institution if mechanical ventilation was initiated prior to admission. Figure 1 depicts the study flow. Numbered study packets, including the data collection tools, were assembled and available. A label was taped to the ventilator on enrollment to indicate group assignment.

The ICU physicians were responsible for all ventilator orders, which included "F_{IO_2} (fraction of inspired oxygen) to maintain specified S_{pO_2} (oxygen saturation measured by pulse oximetry)" for both groups, "initiate weaning protocol" for the PRO group, and individualized ventilator parameter adjustment orders for the PHY group. For PRO group patients, evaluation of patient readiness to wean, ongoing ventilator parameter changes within the protocol, and subsequent evaluation of patient toleration was the responsibility of the ICU respiratory therapist (RT). Within the PHY group, physician-ordered changes in minute ventilation ($\dot{V}_E$), positive end-expiratory pressure (PEEP), and mode were implemented by the ICU therapist. In both groups the ICU therapist and the bedside nurse made F_{IO_2} changes based on pre-established S_{pO_2} parameters.

Physician-Directed Weaning

Patients in the PHY group received physician-directed weaning, which is the standard of care in our institution. The onset and course of weaning were determined by physicians at the attending or fellow level. These patients were weaned according to individual physician preference. Because these physician preferences are unpredictable and include variations not only in method of weaning but also

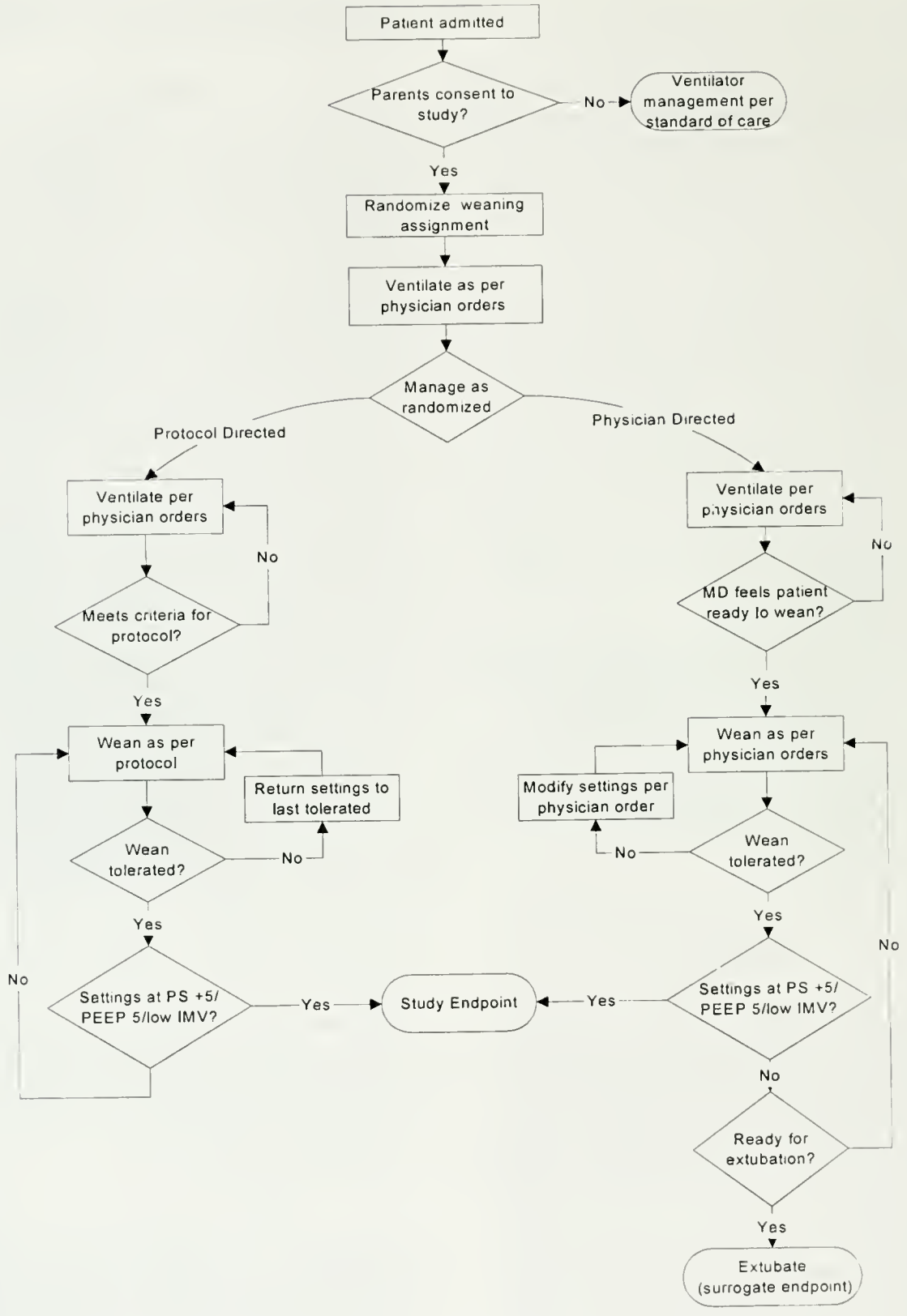


Fig. 1. Patient ventilator management in protocol-directed and physician-directed groups. PS = pressure support. PEEP = positive end-expiratory pressure. IMV = intermittent mandatory ventilation. MD = physician.

in determination of readiness to wean, there were no predetermined criteria for weaning initiation used for the control group. For comparison with the PRO group, the initiation of weaning was defined as the time when a reduction of set $\dot{V}_E$ was made in the presence of normoventilation (pH 7.35–7.45). Physician-directed weaning occurred at any time of day or night.

Protocol-Directed Weaning

Patients in the PRO group were weaned according to an algorithm developed specifically for the purpose of this investigation (Fig. 2). Prior to weaning a patient in this group, the nurse or respiratory therapist (RT) recorded arterial partial pressure of oxygen (when available), F_{IO_2}, S_{pO_2}, PEEP, and respiratory frequency per minute (*f*) every hour. The RT initiated weaning when patients met the following criteria:

- $F_{IO_2} \leq 0.6$
- PEEP $\leq$ 8 cm H_2O
- Total *f* (patient plus ventilator) $\leq$ 1.5 times the predicted value for age, using the mean value
- Ratio of actual to predicted $\dot{V}_E \leq 2$
- pH $\geq$ 7.35 (when arterial blood gas measurement was available)
- S_{pO_2} within the limits established for that patient by the fellow or attending physician
- A chart indicating predicted $\dot{V}_E$ and mean *f* data was provided to the RTs by the investigators

Once the patient met the aforementioned criteria and the RT assigned to the patient established and recorded the presence of spontaneous breathing for 10 consecutive minutes, the critical care attending physician was asked whether he or she had any objection to beginning the weaning protocol. Barring any objection, the patient was placed on SIMV plus PSV. This was considered to be the starting time of the weaning process for purposes of calculating the weaning time. Mechanical *f* was set at 2 breaths/min in patients weighing > 20 kg, and 4 breaths/min in patients weighing $\leq$ 20 kg. Tidal volume was set to achieve 5–7 mL/kg/breath exhaled. The RT determined the level of pressure support, choosing the least amount during which the patient's total *f* did not exceed 1.5 times the predicted *f*. PEEP and supplemental F_{IO_2} were administered as needed in the same fashion as prior to the protocol initiation. Protocol-directed weaning could begin at anytime of day or night, as determined by assessment of readiness.

Criteria for continued weaning, which mimicked the criteria for initiation of weaning, were used throughout the weaning process. Eligibility for continued weaning was assessed and recorded at least once every 4 hours. Each time criteria for weaning were achieved, the RT reduced the amount of pressure support administered in decrements of 2 cm H_2O, as often as every 20 minutes. The pace of weaning was determined by the patient's tolerance of each reduction of pressure support.

Individualized parameters used to indicate patient tolerance included S_{pO_2}, total *f*, pH, and partial pressure of carbon dioxide when available. These were continuously assessed and recorded by the nurse or RT every hour. Ventilator weaning occurred as often as every 20 minutes, provided the criteria were met. Further pressure support weans were held when either (1) the pressure support level reached half the original level recorded at weaning initiation with PEEP $\geq$ 6 cm H_2O, (2) weaning criteria were no longer met, or (3) study end points were achieved. Under the protocol, a patient's pressure support could be increased instead of decreased if for some reason he or she did not tolerate the prior wean.

If PEEP was $\geq$ 6 cm H_2O at the time that pressure support level reached one half of its original level recorded at weaning initiation, and weaning criteria were met, PEEP was reduced by 1 cm H_2O every 30 minutes as tolerated until PEEP reached 5 cm H_2O. Pressure support and PEEP were not weaned at the same time. If PEEP was $\leq$ 5 cm H_2O cm at the time weaning was initiated, no additional PEEP weans were made.

Independent of pressure support weans, the nurse or RT used pre-established S_{pO_2} parameters ordered for each patient to manipulate F_{IO_2}. This is our current standard of care in the PICU and CICU.

When weaning criteria were no longer met, subsequent to a reduction in pressure support, PEEP, or F_{IO_2}, that parameter was increased to the level preceding the most recent wean. If at any time following an increase in a given parameter the criteria were still not met, the patient's physician was notified. In the event that patient intervention required exiting protocol, circumstances were monitored and recorded for the duration of the patient's course of mechanical ventilation.

Study End Points

Our study end point was the time at which minimum settings were achieved: PEEP $\leq$ 5 cm H_2O, pressure support $\leq$ 5 cm H_2O, $F_{IO_2} \leq 0.40$, mechanical rate of 2 or 4 breaths/min (based on patient weight) with patient total *f* $\leq$ 1.5 times the predicted value, ratio of actual to predicted $\dot{V}_E \leq 2$, pH $\geq$ 7.35 (when available), and S_{pO_2} within the limits established for that patient by the fellow or attending physician.

Because there are several reasons that a child could require an artificial airway but not necessarily require continued positive pressure ventilation, minimum settings, rather than extubation, were used to define the end of the weaning period. In addition, our institutional review board felt that extubation as an end point might put patients at

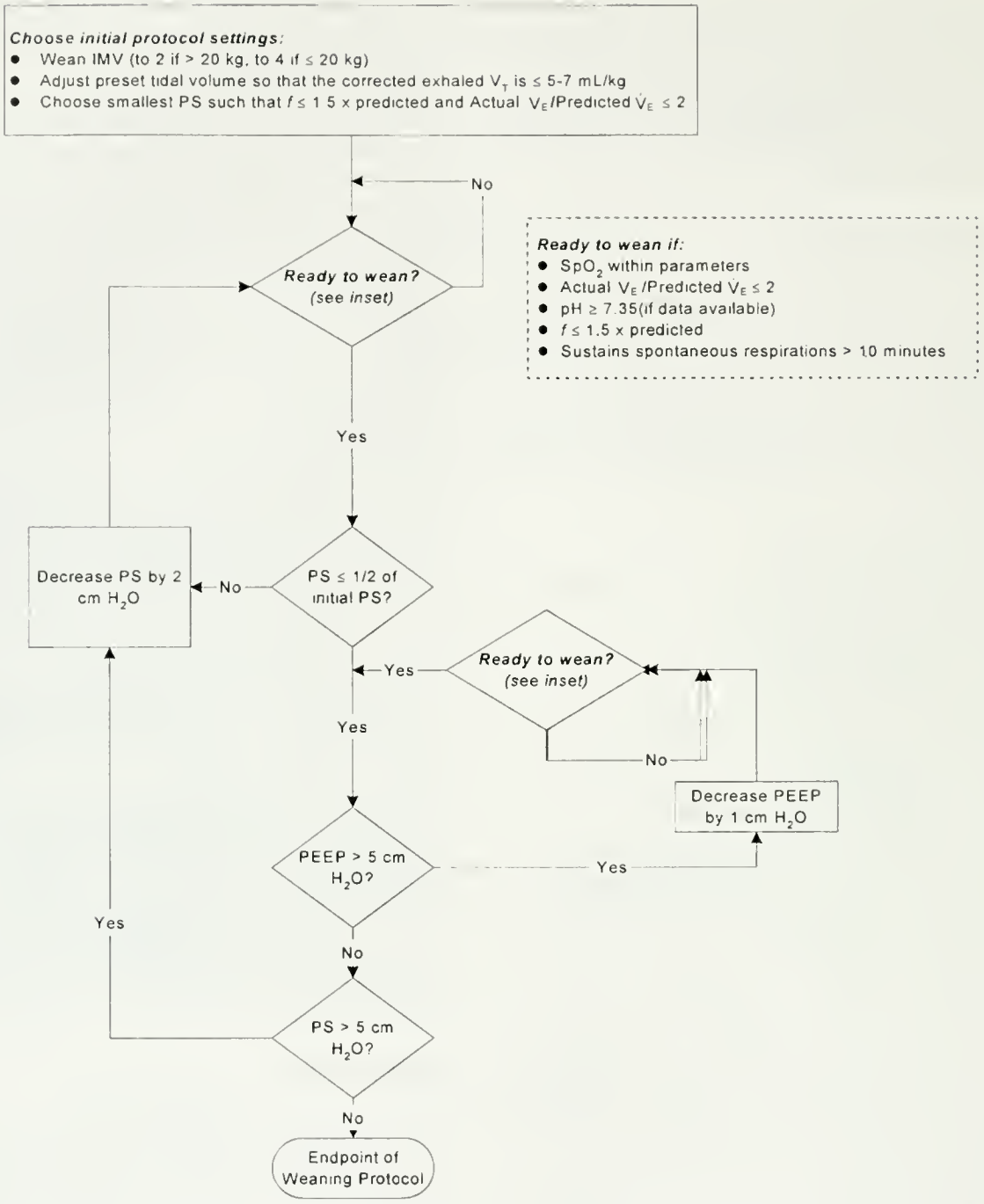

Choose initial protocol settings:
Wean IMV (to 2 if > 20 kg, to 4 if ≤ 20 kg)
Adjust preset tidal volume so that the corrected exhaled V_T is ≤ 5-7 mL/kg
Choose smallest PS such that f ≤ 1.5 x predicted and Actual V_E/Predicted $\dot{V}_E$ ≤ 2
No
Ready to wean? (see inset)
Ready to wean if:
SpO_2 within parameters
Actual V_E /Predicted $\dot{V}_E$ ≤ 2
pH ≥ 7.35(if data available)
f ≤ 1.5 x predicted
Sustains spontaneous respirations > 10 minutes
Yes
Decrease PS by 2 cm H_2O
No
PS ≤ 1/2 of initial PS?
Yes
Ready to wean? (see inset)
No
Yes
Decrease PEEP by 1 cm H_2O
PEEP > 5 cm H_2O?
Yes
Yes
No
PS > 5 cm H_2O?
No
Endpoint of Weaning Protocol

Fig. 2. Protocol-directed weaning: flow diagram of weaning protocol. IMV = intermittent mandatory ventilation. V_T = tidal volume. PS = pressure support. f = respiratory frequency per minute. $\dot{V}_E$ = exhaled minute ventilation. SpO_2 = oxygen saturation measured by pulse oximetry. PEEP = positive end-expiratory pressure.

undue increased risk. At the time we developed the weaning protocol, we had no data about its reliability in terms of determining whether a patient was safe to extubate.

In the PHY group, in the event a patient was extubated prior to reaching the protocol-defined end points, extubation was used as a surrogate for minimum settings.

Data Collection

Along with ventilator settings and ongoing patient assessment, patient data collected included demographics, diagnoses, 12-hour and 24-hour pediatric risk of mortality (PRISM III) scores, time on $F_{IO_2} \geq 0.40$ and ≥ 0.60,

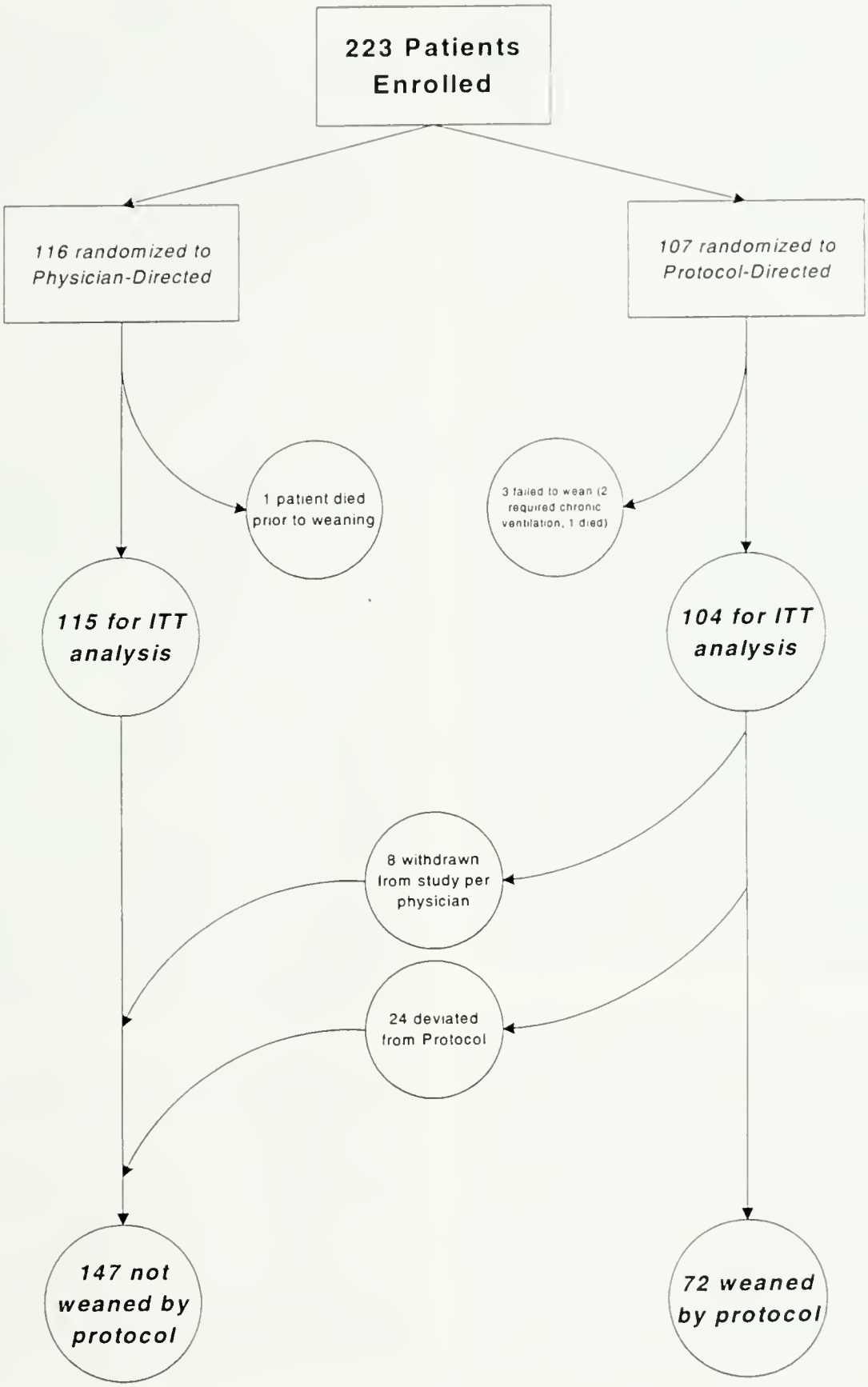

223 Patients Enrolled
116 randomized to Physician-Directed
107 randomized to Protocol-Directed
1 patient died prior to weaning
3 failed to wean (2 required chronic ventilation, 1 died)
115 for ITT analysis
104 for ITT analysis
8 withdrawn from study per physician
24 deviated from Protocol
147 not weaned by protocol
72 weaned by protocol

Fig. 3. Patient enrollment: distribution of patients as randomized and as actually managed. ITT = intent to treat.

number of ICU days, and number of hospital days. Information was also collected on the length of time that patients were on the various phases of mechanical ventilation (eg, weaning), as defined below. The data were maintained in a computerized database (Microsoft Access, Microsoft, Redmond, Washington).

MV_{pre} was the duration of mechanical ventilation prior to initiation of weaning, defined as the length of time between when the patient was intubated in the ICU (or admitted to the ICU intubated) and the time when weaning was initiated. MV_{total} was the total length of time a patient was on mechanical ventilation. *Weaning time* was the time elapsed between initiation of weaning and the time end point criteria were reached. *Extubation time* was the time elapsed between initiation of weaning and the time of extubation.

The indication for intubation and mechanical ventilation was categorized by consensus of the investigators as respiratory or nonrespiratory. A patient was categorized as having a respiratory indication if the disease process involved the lung parenchyma or intrathoracic airways. Examples of respiratory diagnostic indications include bronchiolitis, asthma, pneumonia, acute respiratory distress syndrome, pneumonitis, interstitial lung disease, traumatic lung injury (eg, contusion), and pulmonary edema. Examples of nonrespiratory diagnostic indications included postoperative anesthetic effect, seizure-associated hypoventilation, ingestion-associated hypoventilation, hypoxic ischemic encephalopathy, neuromuscular disorders (eg, infant botulism), scoliosis repair, cerebral contusion or concussion, intracranial hemorrhage, congenital heart disease, and extra-thoracic airway obstruction (eg, croup, laryngotracheomalacia).

Morbidity data collected included rate of reintubation (within 48 h), and incidence of new-onset tracheitis, pneumonia, or subglottic stenosis.

Statistical Analysis

Data were analyzed with commercially available software (Stata, version 6.0, Stata Corporation, College Station, Texas). Outcome variables were analyzed for normality using Shapiro-Wilk and Shapiro-Francia testing. Since almost all variables had non-normal distributions, they were compared by nonparametric analysis with Wilcoxon rank-sum testing. These comparisons were made based on the original intent to treat, as determined by how the patient had been randomized. Some of the analyses were also stratified according to patient care area (PICU versus CICU) and whether the indications for intubation and mechanical ventilation were respiratory or nonrespiratory. Demographic and categorical variables were compared using chi-square and Fisher exact tests.

Results

Data were collected on 223 enrolled patients between May 1998 and February 2000 (Fig. 3). The PHY group had 116 children and the PRO group had 107. Of these, 4 did not reach study end point (2 died after randomization and 2 required prolonged mechanical ventilation). Eight patients were withdrawn from protocol weaning and 24 of the PRO group deviated from protocol. Both the withdrawn and deviation patients were analyzed as randomized. The final analysis was done on 115 patients in the PHY group and 104 in the PRO group (see Fig. 3). Patient withdrawal from the protocol occurred because of physician preference or multidisciplinary educational issues regarding the protocol. No patients exited the protocol because of worsening respiratory failure during weaning that could not be accommodated within the guidelines of the protocol.

The PHY and PRO groups were similar in terms of age, PRISM III scores, and gender distribution (Table 1). We characterized the initial indications for intubation and mechanical ventilation in terms of the primary reason for the respiratory failure or the need for intubation, which are shown in Figures 4 and 5. In both the PHY and PRO groups, the majority of patients required intubation for surgical procedures or for failure of respiratory control (eg, seizure-associated or medication-associated hypoventilation).

Disproportionately more patients were classified as having respiratory diagnoses in the PHY group than in the PRO group (24 versus 7, $p = 0.003$). It is unclear why the distribution of this category in the treatment groups is unequal, especially given that the assignment was random. We were concerned that this might indicate that there was some bias introduced by the fact that only patients in the PRO group were excluded (since the PHY group received standard of care). Because the difference in the incidence of respiratory diagnoses might affect the comparisons of the PHY and PRO groups, we did stratified analyses, which are presented below.

Table 1. Demographic Characteristics

Characteristic	PHY $n = 115$	PRO $n = 104$
Age in years (avg ± SD)	4.19 ± 5.40	5.10 ± 5.71
PRISM III-12 (avg ± SD)	4.04 ± 4.19	3.68 ± 3.59
PRISM III-24 (avg ± SD)	4.83 ± 4.63	4.83 ± 4.45
% male	52.0	56.7
% respiratory diagnoses	20.9	6.7

PHY = physician-directed group
PRO = protocol-directed group
PRISM III-12 = pediatric risk of mortality score at 12 hours
PRISM III-24 = pediatric risk of mortality score at 24 hours

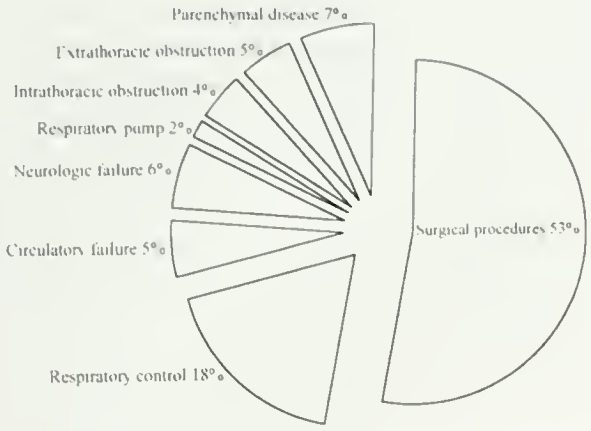


Fig. 4. Indications for intubation in the physician-directed group.

Table 2 shows an unstratified comparison of the PHY and PRO groups in terms of MV_{pre}, weaning time, extubation time, MV_{total}, and total time on $F_{IO_2} \geq 0.40$. Patients in the PRO group overall spent significantly less time in the weaning process and less time from initiation of weaning to extubation. Differences were also present for other variables, but none were statistically significant.

Within each respiratory subgroup, patients on average took longer to wean to end point in the PHY group than in the PRO group (Table 3). There was still a statistically significant difference in weaning time in both diagnostic subgroups, but no significant difference in extubation time in either diagnostic subgroup. We also looked within each treatment group to compare weaning times for respiratory and nonrespiratory diagnoses. As one would expect, for each weaning method, respiratory patients on average took longer to wean than nonrespiratory patients, the difference being statistically significant in the PHY group ($p < 0.001$) and showing a trend in the PRO group ($p = 0.067$).

Thus, many of the overall differences seen between the 2 groups are due to the differences in case mix (respiratory versus nonrespiratory). However, weaning time remained significantly different in the stratified analysis.

Since this study took place in 2 different ICUs (PICU and CICU), there may be a concern that differences between the PHY and PRO groups might be due to factors other than case mix. There is a difference in physician staffing between the 2 units. The PICU is staffed with pediatric intensivists only, whereas the CICU includes pediatric cardiologists and cardiothoracic surgeons as well. However, the PRO and PHY patients were evenly distributed between the 2 units ($p = 0.84$ by chi-square).

Protocol weaning was not influenced by patient location. The difference in weaning times between the nonrespiratory PRO patients in the 2 ICUs was not statistically different (PICU = 6.1 h, CICU = 3.9 h, $p = 0.74$). Nonrespiratory PHY patients had a larger average difference in weaning times between units, but this was not statistically significant (PICU = 20.1 h, CICU = 8.5 h, $p = 0.29$).

There was no difference in morbidity or mortality between the PHY and PRO groups. There was no incidence of new-onset tracheitis, ventilator-associated pneumonia, or subglottic stenosis in either group. Failed extubation (reintubation within 48 h for respiratory indications) was not different between the groups (PRO = 4, PHY = 2). The 2 mortalities seen during the study occurred prior to initiation of weaning and were due to the primary disease process in those patients.

Discussion

As far as we know, prior to this study there were no published studies examining protocol-directed weaning in children. Mechanical ventilation remains a critical component in the management of respiratory insufficiency, central nervous system impairment, and postoperative care of adults and children alike. Because weaning from mechanical ventilation accounts for as much as 40% of the time that a patient receives mechanical ventilation,[1] and because there are many risks associated with prolonging mechanical ventilation,[2] this practice was rated as a high-volume, high-risk process that deserved investigation.

Our main hypothesis was that patients managed by protocol would have a shorter mean duration of mechanical ventilation during the weaning period. We also hypothesized that protocol-guided weaning would be as safe as conventional weaning and that patients managed by protocol would not have a higher incidence of complications and morbidity.

Our data clearly show that weaning time is shorter for patients weaned by protocol, even after stratification for respiratory diagnosis. We used an end point based on minimal mechanical ventilation settings, rather than extuba-

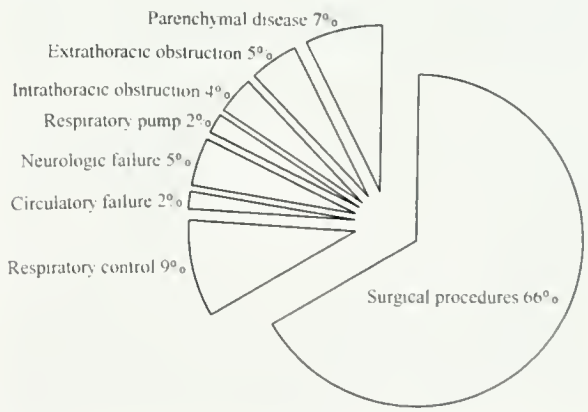


Fig. 5. Indications for intubation in the protocol-directed group.

Table 2. Comparison of Mechanical Ventilation Times

	PHY			PRO			p
	Mean	Median	SD	Mean	Median	SD	
MV_{pre} (h)	52.1	15.0	116.8	33.4	15.5	48.6	0.73
Weaning time (h)	25.2	10.0	39.4	5.9	0.8	12.1	< 0.001
Extubation time (h)	30.1	12.1	46.3	16.2	4.0	32.8	0.004
MV_{total} (h)	116.9	27.5	390.7	47.1	23.8	57.7	0.26
Time on $F_{IO_2} \geq 0.40$ (h)	30.2	3.5	80.7	9.7	3.8	17.9	0.11

PHY = physician-directed group
PRO = protocol-directed group
MV_{pre} = duration of mechanical ventilation prior to initiation of weaning
See text for explanation of weaning time and extubation time.
MV_{total} = total duration of mechanical ventilation
F_{IO_2} = fraction of inspired oxygen

Table 3. Comparison of Mechanical Ventilation Times Stratified for Respiratory Diagnosis Subgroups

	Diagnostic group	PHY			PRO			p
		Mean	Median	SD	Mean	Median	SD	
MV_{pre} (h)	Respiratory	161.2	63.2	217.1	67.3	51.0	80.6	0.31
	Nonrespiratory	23.3	12.2	35.0	31.0	15.3	45.1	0.07
Weaning time (h)	Respiratory	66.4	56.1	59.1	15.7	3.8	25.0	0.01
	Nonrespiratory	14.4	4.1	22.4	5.2	0.7	10.5	< 0.001
Extubation time (h)	Respiratory	76.4	52.8	69.0	33.6	4.2	49.8	0.08
	Nonrespiratory	18.4	5.8	28.9	15.0	4.0	31.2	0.12
MV_{total} (h)	Respiratory	240.1	132.9	242.3	101.2	78.5	89.8	0.16
	Nonrespiratory	84.4	21.8	416.2	43.2	23.0	52.7	0.65
Time on $F_{IO_2} \geq 0.40$ (h)	Respiratory	109.8	30.8	151.2	37.7	13.0	45.0	0.38
	Nonrespiratory	9.2	2.5	16.7	7.7	3.2	12.5	0.69

PHY = physician-directed group
PRO = protocol-directed group
MV_{pre} = duration of mechanical ventilation prior to initiation of weaning
See text for explanation of weaning time and extubation time.
MV_{total} = total duration of mechanical ventilation
F_{IO_2} = fraction of inspired oxygen

tion, because we did not want to exclude patients who needed artificial airways but did not need mechanical ventilation. There were also safety concerns about using an untested protocol to determine whether patients were ready to extubate. This artificial end point did make comparison with the physician-weaned group somewhat more difficult, but in reviewing physician weaning practice during this study, we were able to find end points that were similar to the protocol end point. In nearly half of the PHY group, patients were extubated almost as soon as weaning had started.

For purposes of comparison with other studies, we calculated times from initiation of weaning to extubation as well. There was a significant difference in the overall analysis, with the extubation time shorter for the PRO group. When the analysis was stratified for respiratory diagnosis subgroup, the PRO group still had shorter extubation times, but the difference for respiratory cases only approached significance ($p = 0.08$) and was not statistically significant for nonrespiratory cases. The loss of statistical significance with stratified analysis is most likely due to the difference in case-mix between the PHY and PRO groups (24 PHY respiratory cases versus 7 PRO). It seems that the protocol led to shorter time to extubation, but the study was insufficiently powered to demonstrate a statistically significant difference.

In terms of safety of the protocol, there were no instances of tracheitis, ventilator-associated pneumonia, or subglottic stenosis that occurred after initiation of mechanical ventilation in either group. The incidence of reintubation was slightly higher in the protocol group. Thus, protocol-weaned patients had no higher incidence of morbidity than the physician-weaned patients, although the event rate in both groups was very low.

Our secondary comparisons of other ventilation parameters did not achieve statistical significance, although there were numeric differences. Patients in the study group tended to remain on $F_{IO_2} \geq 0.40$ for less time, although the 2 groups did not differ significantly in total time on $F_{IO_2} \geq 0.40$ ($p = 0.11$).

We thought that MV_{pre} and MV_{total} would be shorter for patients in the PRO group, since they were more actively tested for readiness to wean throughout their time on mechanical ventilation. Although there were numeric differences for both of these parameters, these did not achieve statistical significance in the overall analysis. Interestingly, in the stratified analysis, the difference in MV_{pre} values between the PHY and PRO groups approaches statistical significance ($p = 0.07$) with the nonrespiratory patients, but not with the respiratory patients. We speculate that this reflects that MV_{pre} is influenced not only by increased patient surveillance but also by the degree of respiratory impairment. The increased surveillance makes more of a difference in patients who are intubated for reasons other than parenchymal disease. In these "nonrespiratory" cases, the active reevaluation of patients may make more of a difference in shortening time on mechanical ventilation. The presence of a numeric difference for the respiratory subgroup may be due to less aggressive weaning of PHY group patients because of the nature of their dependence on mechanical ventilation. These same factors may contribute to the lack of statistically significant difference in MV_{total}.

Sedation can impact a patient's ability to wean from mechanical ventilation. We did not explicitly control for sedation, but the random treatment group assignment should have taken care of balancing the groups in terms of sedation approaches. We retrospectively reviewed a random sample of study charts and found that there were similar approaches to sedation in the PRO and PHY groups.

Various ventilator weaning strategies (SIMV versus PSV versus continuous positive airway pressure and T-piece wean) could have been used for the purpose of this comparison. Our study did not compare effectiveness among ventilator weaning types or personnel involved in the implementation of the weaning. The purpose was only to compare a protocol-directed weaning strategy to our traditional physician-directed strategy in pediatric patients.

Future studies of this weaning protocol will include an evaluation of patient population subgroups. By collecting data regarding protocol compliance and variance within each subgroup, we hope to understand the possible difference in outcomes from each. This may show which patient population such a ventilator weaning protocol would serve best. It may also be interesting to see if the criteria for readiness to wean could be simplified or "relaxed."

Conclusions

The protocol-directed weaning strategy developed for the purpose of this investigation resulted in shorter weaning time than physician-directed weaning. This outcome was realized with no increase in morbidity, mortality, or rate of reintubation.

This study has several implications. Our institution has incorporated the use of protocol-directed weaning as a practice change in our PICU and CICU. S_{pO_2} parameters are ordered on an individual patient basis to be used in conjunction with the order for protocol-directed weaning. Giving RTs the ability to streamline ventilator weaning with the aid of a protocol seems effective. Subjective commentary suggests that communication among physician, nursing, and respiratory care personnel may be enhanced, as dialogue between health care providers is crucial to the existence of this program. Although not formally addressed in this analysis, the financial impact of this protocol program must be considered positive as well.

Our environment, where supply and demand for health care services constantly challenges the efficiency of current practices, directed our efforts toward the development of this investigation. The outcome of our prospective randomized comparison of protocol-directed versus physician-directed ventilator weaning proved that protocol-directed weaning resulted in shorter weaning time in these pediatric patients.

REFERENCES

1. Esteban A, Aslfa I, Ibanez J, Benito S, Tobin MJ. Modes of mechanical ventilation and weaning: a national survey of Spanish hospitals. Spanish Lung Failure Collaborative Group. Chest 1994;106(4): 1188–1193.
2. Kollef M, Prang L, Brock W. Reducing the duration of mechanical ventilation: three examples of change in the intensive care unit. New Horizon, 1998;6(1):52–57.
3. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 1995;332(6):345–350.
4. Chao D, Scheinhorn D. Weaning from mechanical ventilation. Crit Care Clin 1998;14(4):799–817.
5. Venus B, Smith RA, Mathru M. National survey of methods and criteria used for weaning from mechanical ventilation. Crit Care Med 1987;15(5):530–533.
6. Saura P, Blanch L, Mestre J, Valles J, Artigas A, Fernandez R. Clinical consequences of the implementation of a weaning protocol. Intensive Care Med 1996;22(10):1052–1056.
7. Kollef MH, Shapiro SD, Silver P, St John RE, Prentice D, Sauer S, et al. A randomized, controlled trial of protocol-directed versus phy-

sician-directed weaning from mechanical ventilation. Crit Care Med 1997;25(4):567–574.
8. Wood G, MacLeod B, Moffatt S. Weaning from mechanical ventilation: physician-directed vs a respiratory-therapist-directed protocol. Respir Care 1995;40(3):219–224.
9. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994;150(4):896–903.
10. MacIntyre NR, Leatherman NE. Mechanical loads on the ventilatory muscles: a theoretical analysis. Am Rev Respir Dis 1989;139(4): 968–973.
11. Tokioka H, Kinjo M, Hirakawa M. The effectiveness of pressure support ventilation for mechanical ventilatory support in children. Anesthesiology 1993;78(5):880–884
12. el-Khatib MF, Chatburn RL, Potts DL, Blumer JL, Smith PG. Mechanical ventilators optimized for pediatric use decrease work of breathing and oxygen consumption during pressure-support ventilation. Crit Care Med 1994;22(12):1942–1948.
13. Rogers MC. Textbook of pediatric intensive care, 3rd ed. Baltimore: Williams & Wilkins: 1996.
14. Khan N, Brown A, Venkataraman S. Predictors of extubation success and failure in mechanically ventilated infants and children. Crit Care Med 1996;24(9):1568–1579.

A Comparison of Two Airway Suctioning Frequencies in Mechanically Ventilated, Very-Low-Birthweight Infants

Leandro Cordero MD, Mercedes Sananes MD, and Leona W Ayers MD

INTRODUCTION: Endotracheal suctioning of mechanically ventilated, very-low-birthweight infants for removal of respiratory secretions can be associated with morbidity. Routine endotracheal suctioning is inadvisable, but the safe minimum endotracheal suctioning frequency for prevention of airway obstruction has not been determined. **HYPOTHESIS:** Decreasing suctioning frequency from every 4 hours to every 8 hours (plus as needed) would have no clinically important effect on the primary outcomes (nosocomial bloodstream infection [BSI], ventilator-associated pneumonia [VAP], and bacterial airway colonization) or secondary outcomes (reintubation rates, need for postural drainage, severity of bronchopulmonary dysplasia [BPD], neonatal mortality, duration of mechanical ventilation, and duration of hospitalization). **METHODS:** We conducted a sequential retrospective study of 90 very-low-birthweight infants who were mechanically ventilated for longer than 7 days and who underwent endotracheal suctioning every 4 hours (plus as needed) and 90 similar infants who underwent endotracheal suctioning every 8 hours (plus as needed). Two-pass endotracheal suctioning used during the study period required predetermined measurement of the suction catheter and prior instillation of saline. **RESULTS:** The 2 treatment groups were similar in demographic and clinical characteristics, including survival (90% and 85%), age at time of death (28 and 33 d), mean birthweight (926 and 934 g), gestational age (27 and 27 wk), duration of ventilation (29 and 27 d), and duration of stay (55 and 53 d). Regardless of suctioning frequency, airway colonization with Gram-positive cocci occurred in the majority of patients by 2 weeks of life. Forty-three percent of the infants suctioned every 4 hours and 44% of those suctioned every 8 hours became airway colonized with Gram-negative bacilli. No Gram-negative bacilli species was more likely to be associated with either treatment group. VAP was diagnosed in 5 of the infants suctioned every 4 hours and in 9 of the infants suctioned every 8 hours. Nosocomial BSI occurred in 18 of the infants suctioned every 4 hours and in 21 of the infants suctioned every 8 hours. The difference in incidence of VAP and BSI was due to a *Pseudomonas aeruginosa* epidemic that started before the change in suctioning frequency. During hospitalization, approximately one fourth of the patients in each group required postural drainage and were reintubated 11 and 10 times per 100 ventilator days, respectively. A comparable number of infants in each group developed severe BPD and were discharged home on oxygen. Suctionings per patient per ventilator day were 6 for the group suctioned every 4 hours and 4 for the group suctioned every 8 hours ($p < 0.01$). **CONCLUSIONS:** A low-frequency suctioning regimen (every 8 hours plus as needed) can be implemented without increasing the incidence of nosocomial BSI, VAP, bacterial airway colonization, frequency of reintubation, need for postural drainage, severity of BPD, neonatal mortality, duration of mechanical ventilation, or duration of hospitalization. Although the minimum suctioning frequency for removal of unwanted respiratory secretions is yet to be established, a substantial reduction in endotracheal suctioning frequency appears to be safe. *Key words: endotracheal suctioning frequency, premature infants, bronchopulmonary dysplasia.* [Respir Care 2001;46(8):783–788]

Introduction

Endotracheal suctioning of mechanically ventilated, very-low-birthweight (VLBW) infants maintains an unobstructed airway by removing accumulated bronchopulmonary secretions. However, endotracheal suctioning has been associated with arterial and venous desaturation,[1,2] cardiac arrhythmia,[3] increased mean arterial and intracranial pressure,[4–7] and transient bacteremia.[8] It is also known that endotracheal suctioning, with or without instillation of saline, can damage the mucosa[9] and impair mucociliary transport,[10] thus rendering the respiratory tract vulnerable to opportunistic infections. To minimize the incidence of these complications, suctioning frequency should be dictated by

Leandro Cordero MD and Mercedes Sananes MD are affiliated with the Department of Pediatrics, and Leona W Ayers MD is affiliated with Allied Medical Professions, The Ohio State University Medical Center, Columbus, Ohio.

Correspondence: Leandro Cordero MD, The Ohio State University Medical Center, N118 Doan Hall, 410 West 10th Avenue, Columbus, OH 43210-1228. E-mail: Cordero-1@medctr.osu.edu.

the patient's condition.[11] The minimum suctioning frequency to maintain airway patency is yet to be determined.[12] Before August 1997, in our neonatal intensive care unit (NICU), endotracheal suctioning was conducted every 4 hours (plus as needed). As of August 1997 we decreased the frequency of suctioning to every 8 hours (plus as needed). This change in respiratory care protocol provided an opportunity to test the hypothesis that decreasing suctioning frequency would have no clinically important effect on primary outcomes (nosocomial bloodstream infection [BSI], ventilator-associated pneumonia [VAP], and bacterial airway colonization) or on secondary outcomes (reintubation rate, need for postural drainage, severity of bronchopulmonary dysplasia [BPD], neonatal mortality, duration of mechanical ventilation, and duration of hospitalization).

Methods

The last 90 consecutively born VLBW infants who stayed on mechanical ventilation longer than 7 days and were suctioned every 4 hours (plus as needed) were compared with the first 90 VLBW infants on mechanical ventilation longer than 7 days but who received endotracheal suctioning every 8 hours (plus as needed). This sequential retrospective investigation was approved by our institutional review board. VLBW infants were defined by a birthweight $\leq$ 1500 g.

On admission to the Level III NICU, all mechanically ventilated infants were considered at risk for early-onset sepsis and were treated with intravenous ampicillin, 100 mg/kg/d, given in 2 doses every 12 hours, and with intravenous gentamicin, 5 mg/kg/d, given according to gestational age, at intervals of 24 hours ($\geq$ 35 wk gestational age) or 48 hours ($<$ 35 wk gestational age). This regimen was continued for 3 days if blood cultures were negative, or for 5 to 7 days if positive. All newborns were treated with a neonatal pressure-limited time-cycled ventilator and, when indicated, with a high-frequency device. Ventilator circuit and humidifiers (dual heated-wire ventilator circuit or Conchaterm III Plus heater [both made by Hudson RCI, Temecula, California] and Airlife Isothermal single or dual heated-wire circuit [Allegiance Healthcare, McGaw Park, Illinois] with a Fisher & Paykel 630 or 730 heater [Fisher & Paykel Health Care, Laguna Hills, California]) were changed every 7 days.

Umbilical arterial catheterization was performed for blood gas monitoring. In those infants who received long-term intravenous therapy, umbilical or central venous catheterizations were also done. Exogenous surfactant (Survanta, Abbott Laboratories, Columbus, Ohio) for treatment of hyaline membrane disease was given at the manufacturer's recommended dose.

Blood culture and complete white cell count were obtained on admission to the NICU. Nosocomial BSI was defined by traditional clinical signs, hematologic abnormalities, and a positive blood culture beginning after 2 days of life. Suspected nosocomial BSI was treated with gentamicin (see above) and vancomycin, 30 mg/kg/d, administered intravenously every 8 hours or every 12 hours. Once blood culture isolates were identified, therapy was changed according to antibiotic susceptibilities. As part of a comprehensive infection control program to monitor airway microbial colonization, bacterial tracheal aspirate cultures were obtained on admission to the NICU and weekly thereafter. After saline solution (0.5 mL) was placed into the endotracheal tube, it was suctioned, collected, and processed immediately, or stored at 4° C for up to 24 hours. Airway bacterial colonization was defined by the presence of Gram-positive cocci and Gram-negative bacilli (GNB) in 2 or more bacterial tracheal aspirate cultures taken at least 1 week apart in infants without clinical or bacteriological evidence of systemic or local infection. In cases of isolation of multiple organisms from the same bacterial tracheal aspirate culture, the bacterial species found more consistently over time was considered the primary colonizer.

BPD was diagnosed clinically in infants with respiratory failure, who were on mechanical ventilation longer than 2 weeks, and who were still treated with oxygen at 28 days of life.[13] According to clinical indications, infants with BPD were given dexamethasone sodium phosphate, 0.5 mg/kg/d, administered intravenously in 2 doses every 12 hours for 3 days, followed by dose tapering. Throughout the study period, no infant received dexamethasone before 7 days of age. Severity of BPD was defined by the need for treatment with oxygen at 36 weeks post-conceptional age and at the time of discharge from the hospital.[14,15] Postural drainage (gentle vibration, body positioning, and endotracheal suction) was done in cases of segmental atelectasis, in an effort to mobilize tracheobronchial secretions.

Chest radiographs were taken of all infants suffering respiratory failure, on admission to the NICU, daily for the first week, biweekly during the second week, and according to clinical needs thereafter. Nosocomial pneumonia was defined by a radiologic diagnosis together with blood and tracheal cultures positive for a respiratory pathogen.[16]

Before August 1997, closed-suction and open-suction catheters were used interchangeably, but after August 1997 a randomized clinical trail was initiated.[17] Eighty-three of the 90 patients in the group receiving suctioning every 8 hours (plus as needed) were randomized into 2 groups (42 closed-suction catheter and 41 open-suction catheter). Comparisons of these 2 groups showed no differences in any clinical or microbiological variables, and, therefore, for the purposes of the present investigation, were considered as one group.

Infants known to desaturate during endotracheal suctioning received a 10% increase in fraction of inspired oxygen prior to the procedure and were returned to pre-suction oxygenation levels shortly thereafter. Two-pass endotracheal suctioning required predetermined measurement of the suction catheter and prior instillation of saline. The size of suction catheter used varied according to endotracheal tube size (6 French for endotracheal tubes of 2.5 mm internal diameter or less and 8 French for larger endotracheal tubes). Open suctioning began with a brief disconnection from the ventilator to allow instillation of 0.3 mL saline into the endotracheal tube. After no more than 6 ventilator breaths, a sterile catheter was introduced to the predetermined length of the endotracheal tube (if mild resistance was encountered, a 1–2 cm withdrawal followed). Suction pressure of 80 mm Hg was applied intermittently while withdrawing the catheter from the airway. This suctioning pass, which was limited to less than 5 seconds, was repeated (rarely more than once) for large, tenacious, or thick secretions.

Closed suctioning began when sterile saline was instilled through the irrigation port a few seconds before the multi-use catheter (Trach Care, Ballard Medical Products, Draper, Utah) control valve was unlocked and the catheter (inside the sheath) was advanced until the predetermined color mark matched the port or until mild resistance was encountered. The catheter was then withdrawn while using intermittent suction pressure of 80 mm Hg for no longer than 5 seconds. Suction pressure and suctioning passes were similar to those described above. The catheter was then irrigated with 0.3 mL of sterile saline at the irrigation port while applying suction. Multi-use catheters were changed daily. Suctioning of the mouth, when needed, was accomplished with a separate, sterile, disposable catheter.

Data Collection and Statistical Analysis

Our NICU was managed under a plan of patient care that did not change during the study period. Tracheal and blood cultures were collected prospectively, and patient demographic and clinical information was obtained from hospital records. Subgroups were formed for specific analysis. The results are reported as mean ± SD for all variables. Unpaired *t* tests were used to analyze the difference of group means for birthweight and gestational age. Duration of mechanical ventilation and duration of hospital stay were compared using the Mann-Whitney test. A chi-square test of proportions and Fisher's exact test were used for noncategorical variables. Power analyses were based on *t* tests for comparing means, and chi-square tests were used to compare percentages. Two-tailed tests were used, with a significance level of $p < 0.05$. This analysis assumed a medium effect size and 90 patients in each of the groups. The resulting power estimate was 0.92. Specific power analyses were conducted for the primary outcome variables. Power to detect large differences was 0.88 for nosocomial BSI, and power to detect medium differences in airway bacterial colonization was 0.80. Because of the low occurrence of VAP, the power to detect increases in VAP incidence was small.

Results

Table 1 presents our comparison of mechanically ventilated VLBW infants who received suctioning either every 4 hours or every 8 hours (plus as needed). Overall survival rate (90 and 85%), mean birthweight (927 and 934 g), mean gestational age (27 and 27 wk), age at time of death (28 and 33 d), duration of mechanical ventilation, duration of stay, and other clinical and demographic variables were not statistically different for the 2 treatment groups. Sixty-five (70%) of the infants suctioned every 4 hours and 60 (64%) of the infants suctioned every 8 hours weighed less than 1000 g at birth.

Analysis of bacterial cultures from 744 tracheal aspirates determined that the patterns of airway bacterial colonization were comparable between the 2 treatment groups. Regardless of treatment group, most tracheal cultures taken during the first week were negative, but by the second week of mechanical ventilation and until final extubation, Gram-positive cocci were isolated alone or in combination with GNB for most bacterial tracheal aspirate cultures. GNB airway colonization was rare during the first 2 weeks.

Table 1. Clinical and Demographic Variables of the Study Population

	Suction Frequency*		p
	Every 4 hours	Every 8 hours	
Patients (*n*)	90	90	
Survivors (*n* and %)	81 (90)	77 (85)	0.23
Birth weight (g)†	926 ± 221	934 ± 200	0.81
Gestational age (wk)†	27 ± 2	27 ± 2	0.08
White/black (*n*)	67/13	69/11	0.52
Male/female (*n*)	48/42	48/42	1.00
Cesarean delivery (*n* and %)	63 (70)	56 (62)	0.12
Exogenous surfactant (*n* and %)	82 (91)	81 (90)	0.73
Dexamethasone (*n* and %)	80 (89)	78 (87)	0.53
Umbilical arterial catheterization (*n* and %)	83 (92)	84 (93)	0.67
Umbilical venous catheterization (*n* and %)	86 (96)	86 (96)	1.00
Broviac catheterization (*n* and %)	25 (28)	20 (22)	0.20
Mechanical ventilation days (*n*)†	29 ± 19	27 ± 16	0.37
Length of stay (d)†	55 ± 24	53 ± 22	0.5

Values are mean ± SD unless otherwise specified
*Plus as-needed
†Evaluated with *t* test. All others evaluated with chi-square test

but became increasingly common during the third week (occurring in 44% of those suctioned every 4 hours and 43% of those suctioned every 8 hours). Environmental flora (*Pseudomonas aeruginosa*, *Serratia marcescens*, and *Acinetobacter baumanii*) were identified in about one fourth of the cases, enteric flora (*Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Escherichia coli*) was found in half, and a combination of several GNB were found in the remaining cases. No GNB species was more likely to be associated with either treatment group.

The number of reintubations per patient (3 ± 3 and 3 ± 2), reintubations per 100 ventilator days (11 and 10), and the need for postural drainage per patient (26 and 24%) were similar. The number of suctionings per patient per ventilator day was significantly less for those suctioned every 8 hours (4 ± 0.7) than for those suctioned every 4 hours (6 ± 0.7) (Table 2). Nosocomial BSI due to coagulase-negative *Staphylococcus* affected 6 of the infants suctioned every 4 hours and 3 of the infants suctioned every 8 hours (all survived). GNB was responsible for 6 BSIs in those suctioned every 4 hours (1 case *P aeruginosa*, 2 cases *E cloacae*, 2 cases *K pneumoniae*, 1 case *E coli*) and 11 in those suctioned every 8 hours (5 cases *P aeruginosa*, 3 cases *K pneumoniae*, 3 cases *E coli*). VAP was diagnosed in 5 of those suctioned every 4 hours and in 9 of those suctioned every 8 hours. *P aeruginosa* was the pathogen identified in 8 cases (all died), *K pneumoniae* in 3 cases (all survived), *E cloacae* in 2 cases (all survived), and *E coli* in 1 case (died). Nosocomial BSI and VAP cases due to *P aeruginosa* occurred during an 8-month outbreak that started shortly before changing the endotracheal suctioning regimen. There were 2 candidemia cases among those suctioned every 8 hours.

Table 2. Outcome Variables

	Suctioning Frequency*		p
	Every 4 hours	Every 8 hours	
Patients (*n*)	90	90	
Suctionings/patient/day (*n*)†	6 ± 0.7	4 ± 0.7	0.001
Reintubations/patient (*n*)†	3 ± 3	3 ± 2	0.28
Reintubations/100 ventilator days (*n*)	11	10	0.74
Patients with postural drainage (*n* and %)	23 (26)	22 (24)	0.46
BSI due to Gram-positive cocci (*n*)	12	8	0.14
BSI due to Gram-negative bacilli (*n*)	6	11	0.10
BSI due to fungus (*n*)‡	0	2	0.50
Ventilator-associated pneumonia (*n*)	5	9	0.16
Survivors discharged home on O_2 (*n* and %)	43 (53)	46 (60)	0.24

Values are mean ± SD unless otherwise specified
*Plus as-needed
†Evaluated with *t* test
BSI = blood stream infection
‡Evaluated with Fisher's exact test
Values not evaluated with *t* test or Fisher's exact test were evaluated with chi-square test

Table 3. Nosocomial Infections, Primary Pathogens

	Suctioning Frequency			
	Blood Stream Infection		Ventilator-Associated Pneumonia	
	Every 4 hours	Every 8 hours	Every 4 hours	Every 8 hours
Pseudomonas aeruginosa[a]	1	5	3	5
Klebsiella pneumoniae	2	3	1	2
Enterobacter cloacae	2	0	1	1
Escherichia coli	1	3	0	1
Candida albicans	0	2	0	0
Staphylococcus epidermidis and *Staphylococcus hominis*	6	3	0	0
Staphylococcus aureus	5	1	0	0
Enterococcus faecalis	1	3	0	0
Multiple organisms	0	1	0	0
Total	18	21	5	9

[a]Epidemic

Considering the entire group of patients, 43 (48%) of those suctioned every 4 hours and 46 (51%) of those suctioned every 8 hours were on supplemental oxygen at 36 weeks post-conceptional age. At the time of discharge home, the number of infants on oxygen was 43 (53%) in those suctioned every 4 hours and 46 (60%) in those suctioned every 8 hours (see Table 2).

Discussion

Shortly after intubation, the inside of the endotracheal tube colonizes with oropharyngeal or respiratory flora. Most bacteria, especially slime-producing species, develop a biofilm that supports the persistence of a substantial number of microorganisms. Bacterial colonization of the respiratory tract of the mechanically ventilated VLBW infant is an issue aside from the incidence of nosocomial infection. Previous studies have shown that airway colonization with GNB associates with lung injury in baboons[18] and with the severity of BPD in humans.[19] Repeated endotracheal suctionings, particularly after saline instillations,[20] could dislodge bacteria into the trachea[21] and lower respiratory system. Although the pathogenesis is still uncertain, it is possible that lung hyperinflation (ie, bagging) facilitates hematogenous dissemination of bacteria present in the lower airways and alveoli.[22] Although the number of suc-

tionings per ventilator day in this study was significantly less among those suctioned every 8 hours, the incidence, type, and pattern of airway bacterial colonization was not different for the 2 treatment groups.

Bloodstream infection and VAP, the most common nosocomial infections among NICU patients, are strongly associated with duration of mechanical ventilation, infant birthweight, duration of hospital stay, and the presence of indwelling arterial and venous catheters.[23,24] The higher occurrence of nosocomial BSI and VAP in those infants suctioned every 8 hours is attributable to a *P aeruginosa* epidemic that started shortly before the change to the every-8-hours suctioning regimen. Except during the epidemic, the rate of nosocomial infections (BSI and pneumonia) did not appear to be affected by the change in suctioning frequency.

Secretion occlusion of the endotracheal tube and accidental tube dislodgement are the most common reasons for reintubation. That suctioning frequency can be lowered without increasing the frequency of reintubation suggests that respiratory secretions can be successfully managed with an every-8-hour suctioning regimen. Considering the size of our patients, the severity of their BPD, and the duration of their mechanical ventilation, it is not surprising that almost one fourth of the patients in both treatment groups required some chest physical therapy (postural drainage) during hospitalization. Since there was no difference between the treatment groups in the need for postural drainage, it can be inferred that segmental atelectasis occurred with similar frequency in both treatment groups.

Tracheal intubation interrupts the transport of respiratory secretions up the mucociliary escalator, allowing mucus accumulation and inspissation within the endotracheal tube, leading to partial or complete tube obstruction. Thus, endotracheal suctioning helps, in some cases, to maintain an unobstructed airway. Few studies dealing with endotracheal tube occlusion in neonates[25,26] were done before the availability of exogenous surfactant and modern ventilator technology. Visible secretions in the endotracheal tube, acute oxygen desaturations, change in quality of breath sounds, and quantitative and qualitative changes in respiratory secretions constitute objective criteria for endotracheal suctioning.[27] There is consensus that routine suctioning is no longer justified and that suctioning frequency should be individualized.[11,28,29] A survey of pediatric intensive care nurses, however, found that though 76% of 82 respondents agreed with the concept of "as needed" endotracheal suctioning, almost half of them reported suctioning their intubated patients routinely every 2 hours.[30] This contradiction between knowledge and practice may be explained by nursing preference for routine orders, and highlights the need for specific educational efforts.[31]

For adults and infants,[1–8] there is abundant literature regarding systemic and local adverse effects of endotracheal suctioning, but surprisingly little is known about their prevention.[17] Our results indicate that a substantial reduction in the frequency of endotracheal suctioning (change from every 4 hours to every 8 hours, plus as needed) can be implemented without increasing bacterial airway colonization, frequency of reintubation, need for postural drainage, duration of mechanical ventilation, duration of hospitalization, incidence of VAP, incidence of nosocomial BSI, severity of BPD, or neonatal mortality.

To our knowledge, only one group of investigators reported a safe decrease in frequency of endotracheal suctioning. That report, however, is not comparable to ours, since it deals only with neonates during the first 3 days of life, rather than with neonates undergoing prolonged ventilation.[32] Our study population was composed of VLBW infants who developed chronic lung disease and were at higher risk for nosocomial BSI, airway colonization with GNB, and pneumonia. Purulent respiratory secretions, one of the most commonly cited reasons for endotracheal suctioning, occur more often with GNB airway colonization.[33] However, for these high risk VLBW infants undergoing prolonged ventilation, reduced suctioning frequency, over a more extended period than previously reported, can be practiced without adversely affecting primary or secondary outcomes.

Conclusions

An every-8-hours (plus as needed) endotracheal suctioning protocol can be implemented without increasing adverse clinical events or neonatal mortality. Endotracheal suctioning should be done as rarely as possible but as frequently as needed. Respiratory and nursing care plans for maintaining airway patency in mechanically ventilated VLBW infants need to be updated based on current knowledge.

ACKNOWLEDGEMENTS

Thanks to Larry M Sachs PhD of The Ohio State University College of Medicine, for statistical consulting.

REFERENCES

1. Simbruner G, Coradello H, Fodor M, Havelec L, Lubec G, Pollak A. Effect of tracheal suction on oxygenation, circulation, and lung mechanics in newborn infants. Arch Dis Child 1981;56(5):326–330.
2. Kerem E, Yatsiv I, Goitein KJ. Effect of endotracheal suctioning on arterial blood gases in children. Intensive Care Med 1990;16(2):95–99.
3. Johnson KL, Kearney PA, Johnson SB, Niblett JB, MacMillan NL, McClain RE. Closed versus open endotracheal suctioning: costs and physiologic consequences. Crit Care Med 1994;22(4):658–666.
4. Durand M, Sangha B, Cabal LA, Hoppenbrouwers T, Hodgman JE. Cardiopulmonary and intracranial pressure changes related to endotracheal suctioning in preterm infants. Crit Care Med 1989;17(6):506–510.

5. Perlman JM, Volpe JJ. Suctioning in the preterm infant: effects on cerebral blood flow velocity, intracranial pressure, and arterial blood pressure. Pediatrics 1983;72(3):329–334.
6. Shah AR, Kurth CD, Gwiazdowski SG, Chance B, Delivoria-Papadopoulos M. Fluctuations in cerebral oxygenation and blood volume during endotracheal suctioning in premature infants. J Pediatr 1992;120(5):769–774.
7. Segar JL, Merrill DC, Chapleau MW, Robillard JE. Hemodynamic changes during endotracheal suctioning are mediated by increased autonomic activity. Pediatr Res 1993;33(6):649–652.
8. Storm W. Transient bacteremia following endotracheal suctioning in ventilated newborns. Pediatrics 1980;65(3):487–490.
9. Sackner MA, Landa JF, Greeneltch N, Robinson MJ. Pathogenesis and prevention of tracheobronchial damage with suction procedures. Chest 1973;64(3):284–290.
10. Landa JF, Kwoka MA, Chapman GA, Brito M, Sackner MA. Effects of suctioning on mucociliary transport. Chest 1980;77(2):202–207.
11. Wood CJ. Endotracheal suctioning: a literature review. Intensive Crit Care Nurs 1998;14(3):124–136.
12. Simmons CL. How frequently should endotracheal suctioning be undertaken? Am J Crit Care 1997;6(1):4–6.
13. Hansen TWR, Wallach M, Dey AN, Boivin P, Vohr B, Oh W. Prognostic value of clinical and radiological status on day 28 of life for subsequent course in very low birthweight (< 1,500g) babies with bronchopulmonary dysplasia. Pediatr Pulmonol 1993;15(6):327–331.
14. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82(4):527–532.
15. Sinkin RA, Cox C, Phelps DL. Predicting risk for bronchopulmonary dysplasia: selection criteria for clinical trials. Pediatrics 1990;86(5):728–736.
16. Cordero L, Coley BD, Hogan MJ, Ayers LW. Radiological pulmonary changes during Gram-negative bacillary nosocomial bloodstream infection in premature infants. J Perinatol 1998;18(4):291–296.
17. Cordero L, Sananes M, Ayers LW. Comparison of closed (Trach Care MAC) with an open endotracheal suction system in small premature infants. J Perinatol 2000;20(3):151–156.
18. Coalson JJ, Gertsmann DR, Winter VT, Delemos RA. Bacterial colonization and infection studies in the premature baboon with bronchopulmonary dysplasia. Am Rev Respir Dis 1991;144(5):1140–1146.
19. Cordero LW, Ayers L, Davis K. Neonatal airway colonization with Gram negative bacilli: association with severity of bronchopulmonary dysplasia. Pediatr Infect Dis J 1997;16(1):18–23.
20. Hagler DA, Traver GA. Endotracheal saline and suction catheters: sources of lower airway contamination. Am J Crit Care 1994;3(6):444–447.
21. Sottile FD, Marrie TJ, Prough DS, Hobgood CD, Gower DJ, Webb LX, et al. Nosocomial pulmonary infection: possible etiologic significance of bacterial adhesion to endotracheal tubes. Crit Care Med 1986;14(4):265–270.
22. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ. Effect of mechanical ventilation strategy on dissemination of intratracheally instilled *Escherichia coli* in dogs. Crit Care Med 1997;25(10):1733–1743.
23. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infection Surveillance System. Pediatrics 1996;98(3 Pt 1):357–361.
24. Moore DL. Nosocomial infections in newborn nurseries and neonatal intensive care units. In: Mayhall CG, editor. Hospital epidemiology and infection control. Baltimore: Maple Press; 1996:535–564.
25. Redding GJ, Fan L, Cotton EK, Brooks JG. Partial obstruction of endotracheal tubes in children: incidence, etiology, significance. Crit Care Med 1979;7(5):227–231.
26. Prendiville A, Thomson A, Silverman M. Effect of tracheobronchial suction on respiratory resistance in intubated preterm babies. Arch Dis Child 1986;61(12):1178–1183.
27. Wood CJ. Can nurses safely assess the need for endotracheal suction in short-term ventilated patients, instead of using routine techniques? Intensive Crit Care Nurs 1998;14(4):170–178.
28. AARC Clinical Practice Guideline. Endotracheal suctioning of mechanically ventilated adults and children with artificial airways. Respir Care 1993;38(5):500–504.
29. McKelvie S. Endotracheal suctioning. Nurs Crit Care 1998;3(5):244–248.
30. Swartz K, Noonan DM, Edwards-Beckett J. A national survey of endotracheal suctioning techniques in the pediatric population. Heart Lung 1996;25(1):52–60.
31. Copnell B, Fergusson D. Endotracheal suctioning: time-worn ritual or timely intervention? Am J Crit Care 1995;4(2):100–105.
32. Wilson G, Hughes G, Rennie J, Morley C. Evaluation of two endotracheal suction regimes in babies ventilated for respiratory distress syndrome. Early Hum Dev 1991;25(2):87–90.
33. Cordero L, Sananes M, Dedhiya P, Ayers LW. Purulence and Gram-negative bacilli in tracheal aspirates of mechanically ventilated very-low-birthweight infants. J Perinatol 2001; 21: in press.

An Evaluation of Ventilator Reliability: A Multivariate, Failure Time Analysis of 5 Common Ventilator Brands

Paul B Blanch RRT

INTRODUCTION: Mechanical ventilator failures expose patients to unacceptable risks and are expensive. By identifying factors that correlate with the amount of time between consecutive ventilator failures, we might reduce patient risk, save money, and shed light on a number of important questions concerning whether reliability changes as a function of time. **OBJECTIVE:** Investigate the correlation between several explanatory variables and the time between consecutive ventilator failures and address the following questions: (1) Are ventilators as safe and reliable following repairs as they were before failing? (2) Does reliability change significantly as a ventilator is used or ages? (3) Does a hospital's particular operating environment play a role in ventilator reliability? (4) Are ventilator service contracts worth the money? **METHODS:** A retrospective review was conducted using repair and maintenance records from 2 hospitals: a 570-bed teaching hospital and a 410-bed local community hospital. Records were examined from a total of 66 individual ventilators, of 5 different brands, used between July 1, 1991, and January 3, 2001. The ventilators included 13 Tyco-Mallinckrodt Infant Star, 10 Bird VIP, 11 Bird 6400ST, 16 Bird 8400STi, and 16 Tyco-Mallinckrodt 7200ae. The dependent variable was the operating time between or before unexpected mechanical failures; this was determined by the difference between hours logged on the ventilator hour meter at the time of failure and that recorded when the study began, or when the ventilator was new. Thereafter (when applicable), the time before failure was the difference in hours at consecutive failures. Seven independent explanatory covariates were selected and analyzed as potential correlates with time between failures. Another independent variable, the site of ventilator use (community or teaching hospital), was also tested for significance. Data were analyzed using the Cox proportional hazard model, the multiple-groups survival statistic, and the Cox-Mantel test. **RESULTS:** In 2,567,365 hours of ventilator operation, 290 observations were recorded (226 failures and 64 censored observations). Two of the 7 covariates were judged time-dependent, excluded from the Cox model, and evaluated using other techniques. Of the 5 remaining covariates, 2 were significantly related to reliability, both indirectly. There was no difference in reliability, regardless of how many times a ventilator had been previously repaired, but hospital environment did significantly affect reliability. **CONCLUSIONS:** Ventilator reliability depends on a number of factors. This study indicates that, on average, ventilator reliability improves the more a ventilator is used and the longer the brand has been commercially available. The number of previous ventilator repairs did not affect reliability, but the hospital environment did. These data, if validated, should help to enhance our understanding of ventilator reliability and could eventually have profound economic and safety implications as well. *Key words: ventilator reliability, ventilator failure, ventilator maintenance, mechanical failure.* [Respir Care 2001;46(8):789–797]

Introduction

A reasonable estimate suggests that today, one third to one half of all intensive care unit patients receive ventilatory support during their hospital stays.[1] In the United States alone, 50,000 mechanical ventilators are currently in use (100,000 or more worldwide).[2] Further estimates suggest that in the United States as many as 1.5 million patients receive some form of ventilatory support outside of operating and recovery rooms each year.[2,3] With so many ventilators in use, a large number of mechanical failures seems inevitable.

Modern mechanical ventilators represent a large capital expense for most hospitals (at $10,000–30,000 each, or more),[2] are costly to repair ($1,000 or more per repair),[4] and their maintenance often requires a considerable invest-

Paul B Blanch RRT is affiliated with the Department of Anesthesiology, University of Florida College of Medicine, and Respiratory Care Services, Shands Hospital at the University of Florida, Gainesville, Florida.

The author has no financial interest in any product or potential product described.

Correspondence: Paul B Blanch RRT, Department of Anesthesiology, University of Florida College of Medicine, PO Box 100254, Gainesville FL 32610-0254. E-mail: blancpb@shands.ufl.edu.

ment of time and money. More importantly, unexpected ventilator failures expose the patient to potential harm; the risks can be considerable.[5,6] While there are now some data quantifying the *average* reliability of several common ventilators,[7] there are no data identifying which factors, if any, are correlated with ventilator reliability or what happens to reliability as a ventilator ages or is used extensively. Unbiased information of this type is important for a number of reasons. First, individual ventilators or ventilator brands prone to failure represent poor investments, particularly over time. Moreover, if ventilator reliability changes as ventilators age, an initially reliable brand may become less reliable as it ages, or vice-versa. Some hospitals attempt to avoid unexpected repair costs as ventilators age by purchasing a service contract for each ventilator, yet there are no compelling data to suggest whether such contracts actually save money. Another important issue involves determining how long, on average, ventilators can be used safely before they require replacement. In addition, ventilator manufacturers often suggest that the environment in which a ventilator is operated—factors such as a hospital's compressed air quality or the severity and frequency of electrical power disruptions—can strongly influence a ventilator's reliability, but is this accurate? Finally, there remains another, unproven premise involving mechanical ventilators,[7] which is that administrators, clinicians, and risk managers all tacitly assume that, following each repair, a mechanical ventilator is as safe and reliable as it was when new. Is this a reasonable and valid assumption? Or does the risk of unexpected ventilator failure increase following one, two, or multiple failures?

The present study was designed to analyze the relationship between ventilator reliability, as measured by the time before failure, and a number of independent variables—factors potentially related to reliability, such as chronological age and the number of previous failures. The main objective is to shed light on or answer directly some of the unanswered questions involving the reliability of the current generation of mechanical ventilators.

Methods

The study consisted of a retrospective review and analysis of repair and maintenance records for 5 brands of mechanical ventilators maintained and used at 2 hospitals: a 570-bed, university-affiliated hospital with physician, nursing, pharmacy, and respiratory therapy training programs, and a 410-bed community hospital. A total of 66 ventilators were studied: 13 Tyco-Mallinckrodt Infant Star (STAR), 10 Bird VIP (VIP), 11 Bird 6400ST (6400ST), 16 Bird 8400STi (8400STi) (all Bird ventilators made by Thermorespiratory Group, Palm Springs, California), and 16 Tyco-Mallinckrodt 7200ae (7200ae) (Tyco-Mallinckrodt, Carlsbad, California). Each ventilator was used for some portion of or throughout the period beginning July 1, 1991, and ending January 3, 2001. Ventilators of the studied brands purchased during the course of the study were added into the study on the date they were placed into use. Once in the study, each ventilator was either ready for use or in use throughout the remainder of the study (except for time out for troubleshooting, repairs, or calibration). The chronological age of each ventilator (in years) was determined by using the month and year the ventilator was first available for use in the hospital as day 1. Institutional repair and maintenance records were obtained for each of the studied ventilators and used to determine the date each ventilator was first placed into service, the date each reported failure was noted, the total operating hours logged on the hour meter at the start of the study or when placed into use, and the hours logged the day each failure was reported. For the purpose of the study, a failure was defined as any unexpected problem that rendered a ventilator inoperable or unsafe to use until it was either repaired or recalibrated by a biomedical engineer or factory-certified technician. Documented minor repairs, often performed by bedside clinicians, were excluded. Using this information, the dependent variable (the time before failure, or the number of hours each ventilator operated before experiencing a failure) was determined. Because most ventilators experienced several failures during the course of the study, the dependent variable, also included observations recorded as the number of hours a ventilator operated without incident between consecutive failures. For this study the data were right-censored. That is, at the conclusion of the study it was not known how long each ventilator would continue to operate before failing (again, in most cases). For that reason, the time between the last documented failure and the conclusion of the study was considered a censored event, except for those ventilators awaiting repairs when the study ended.

There are a number of independent variables or covariates that potentially correlate with the dependent variable; a practical list, which is neither complete nor exhaustive, was formulated (Table 1). Each of these variables was evaluated separately for each observed failure and then analyzed as a prognostic covariate.

Manufacturers provided (1) the month and year each studied brand of ventilator was first commercially available, (2) the suggested retail price of a fully equipped version of each studied brand of ventilator (including a graphics monitor if applicable), and (3) the recommended preventive maintenance retail costs (all in 2001 dollars).

Statistical Analysis

To determine frequency distribution best describing the study data, the data were compared against the 4 common, nonlinear, distribution models generally associated with

Table 1 Definition of Prognostic Variables

1. Age	Ventilator chronological age, measured in years of use
2. Brand	Ventilator brand (eg, VIP or STAR)
3. Purchase price	Suggested retail cost (2001 dollars) for a fully-equipped version of a ventilator brand, including a graphic monitor if applicable
4. Failures	Number of previous failures/repairs
5. Maintenance cost	Suggested retail cost (2001 dollars) for preventive maintenance of a ventilator brand each 10,000 hours of usage
6. Product age	Number of years since a specific ventilator brand was first released for sale
7. Site	Site of ventilator use—community or teaching hospital
8. Use	Ventilator use, measured in hours of operation

survival or time before failure data. Because time before failure data sets generally assume a nonlinear frequency distribution and contain censored observations, correlations were tested for using the standard Cox proportional hazard multiple regression model.[8,9] This particular approach is exceptionally practical for such data sets because it makes no assumptions concerning the underlying frequency distribution of the data. The standard Cox model, however, assumes that each prognostic covariate incorporated into the model satisfies the so-called proportional hazard assumption.[8] The validity of that assumption was tested individually for each studied covariate, using the log-log Kaplan-Meier graphical approach.[8] Covariates judged as time-dependent (not satisfying the proportional hazard assumption) were noted, omitted from the multiple regression model, and analyzed separately.

The dichotomous covariate, site (see Table 1), was also omitted from the multiple regression model because under normal circumstances it does not represent a variable. Although the location of use *was* a variable in this particular study, as a general rule ventilators are used only at the facility (eg, hospital or medical center) owning them. Significance for this covariate was tested for by separating the time before failure data into 2 groups, based on the location of use (teaching or community hospital). A second test for significance was made by removing any ventilator brands, from either group, not in use at both facilities. The hypothesis that the time before failure was not different at the 2 study locations was tested using the Cox-Mantel test.

Based on strong evidence of nonparallelism seen on the relevant Kaplan-Meier plots, both the brand and use variables were determined to be time-dependent. To investigate this situation, data for each of the 5 brands of ventilator were divided into 3 groups, based on use:

1. Failures that occurred in the first 15,000 hours of ventilator operation (use).

2. Failures that occurred in the time period from 15,001 to 30,000 hours of ventilator operation.

3. Failures that occurred after 30,001 hours of ventilator operation.

For each of the 5 ventilator brands, the time before failure in each of these 3 groups was compared against each other group, using the survival statistic for multiple groups. When differences were noted, multiple comparisons were performed using the Cox-Mantel test.

Throughout the statistical analysis, α was set at 0.05 for statistical significance. All descriptive statistics, hypothesis testing, and graphical analysis were performed with commercially-available software (STATISTICA for Windows, version 5.5A, StatSoft, Tulsa, Oklahoma).

Results

During the 9.5-year study, the 66 study ventilators operated for a combined total of 2,567,365 hours. During that period, 290 observations were recorded (Table 2). The average ventilator survived 8,857 hours of use before experiencing an unexpected mechanical failure. Table 3 shows statistical data for the 7 continuous study variables. The study data differed significantly from all of the common failure time distribution models (exponential, linear hazard, and Gompertz),[8] except 2 weighted versions of the decreasing Weibull distribution model (Fig. 1).

Based on the Cox proportional hazard model, there was no significant relationship between the covariates failures, purchase price, maintenance cost, and the dependent variable, time before failure. However, both of the variables—chronological age ($p < 0.0001$) and product age ($p < 0.0001$)—were strongly but inversely related to the time before failure. That is, as the magnitude of either of those variables increased, the cumulative frequency of unexpected failure decreased.

Ventilators used at the community hospital were significantly more reliable than those used at the teaching hospital ($p = 0.0004$) when all brands were compared, and also significantly more reliable ($p = 0.0003$) when only those brands used at both hospitals were compared.

There were also many significant differences noted when the relationship between the 2 time-dependent covariates, ventilator brands and use, were analyzed (Fig. 2). For several ventilators (STAR, VIP, and 6400ST), the time before failure was significantly improved at each of 3 increasing levels of use tested. The 8400STi improved dramatically from the first level to the second, but showed no difference thereafter. Only the 7200ae showed no difference in the time before failure between any of the use levels tested.

Table 2. Ventilator Data

Brand*	STAR	VIP	6400 ST	7200ae	8400STi	Results
Number of ventilators	13	10	11	16	16	66 (Total)
Failures (n) (censored observations)	46 (13)	22 (10)	56 (11)	74 (14)	30 (16)	226 (64) (Totals)
Time before failure: total (h)	8,303 ± 8,990	7,595 ± 7,266	5,879 ± 6,191	10,071 ± 9,784	12,513 ± 10,477	8,857 ± 8,986 (Mean ± SD)
Use during study: average (h)	498,810	243,099	393,881	857,090	574,485	2,567,365 (Total)
Use/ventilator/year† (h)	5,119	4,021	3,632	6,522	5,038	5,098 (Mean)

*Ventilator brands and manufacturers are described in the text.
†Because all ventilators did not participate for the entire study, averages were obtained by averaging the hours of use divided by the years of participation for each ventilator.

Table 3. Continuous Study Variables

Variable	Variable Type	Mean	Standard Deviation	Minimum	Maximum	Time-Dependent
Age (y)	Independent	6.69	3.97	0.08	17.8	No
Failures (n)	Independent	2.52	2.56	0	14	No
Maintenance cost ($)	Independent	2,778.7	237.96	2,430	3,220	No
Product age (y)	Independent	11.13	3.93	1.0	18.1	No
Purchase price ($)	Independent	18,650.6	4,911.5	10,500	23,675	No
Use (h)	Independent	33,098	23,060	44	103,908	Yes
Time before failure (h)	Dependent	8,856.9	8,985.9	19	46,585	NA

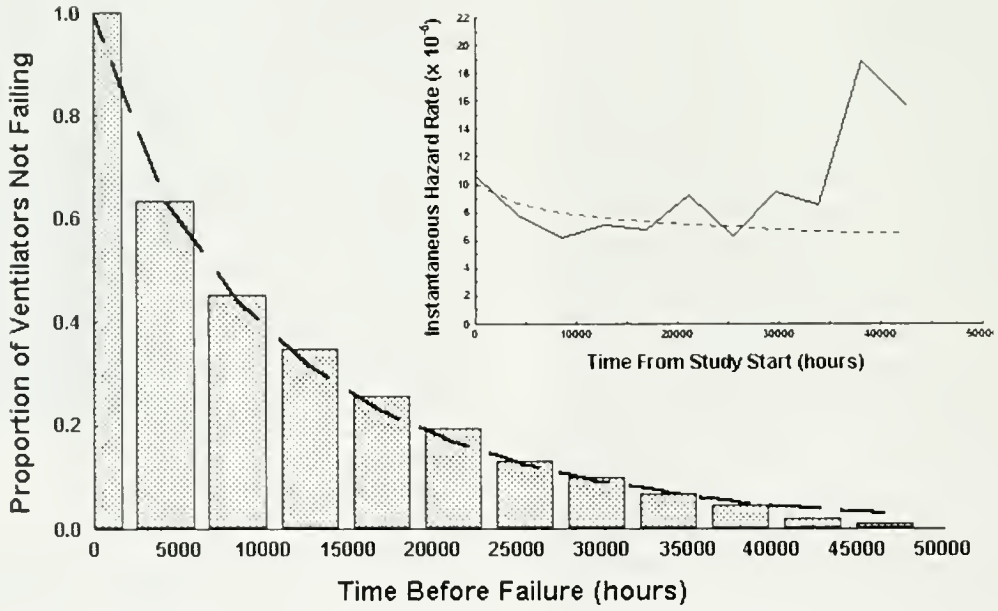


Fig. 1. Cumulative frequency distribution histogram plotting a series of 12 equal intervals of time before failure against the proportion of ventilators not having yet experienced a mechanical failure (or still surviving) within each time interval during the study. The appropriate frequency distribution model for the data is determined by the best-fit hazard function (insert). The actual hazard function plot (solid line) is not statistically different ($p = 0.117$) from a weighted, decreasing Weibull function (dotted line). A representative decreasing Weibull survival curve of the form

$$S(t) = ae^{-ab}bt^{(b-1)}$$

(wherein S(t) is survival time, a and b are parameters of the distribution, t = time, and e = 2.718) is shown superimposed on the actual hazard function.

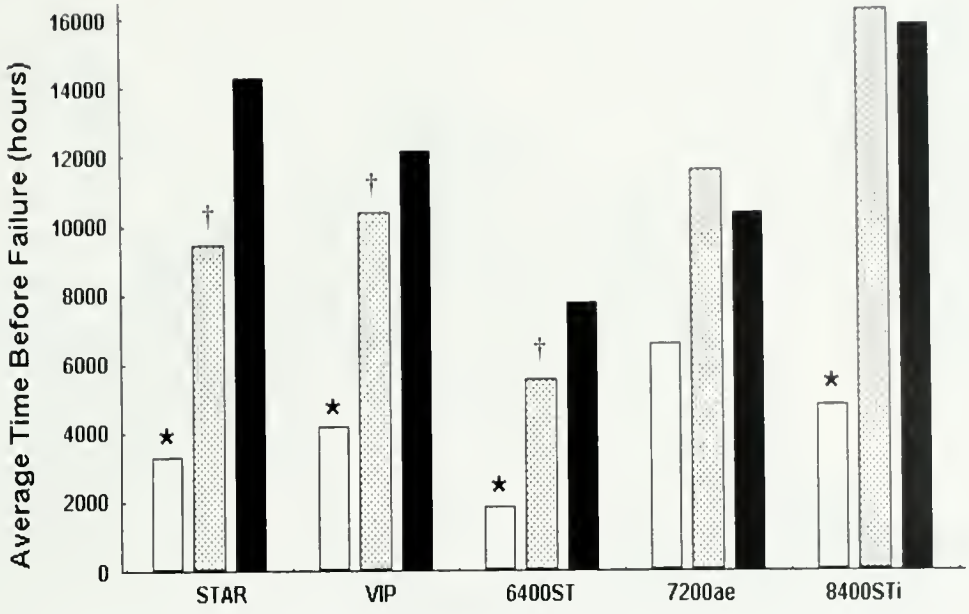


Fig. 2. Average time before ventilator failure for each of the 5 ventilator brands studied. Failure data for each ventilator brand was subdivided into 3 groups: (1) failures occurring in the first 15,000 hours of use (white columns), (2) failures occurring between 15,001 and 30,000 hours of use (stippled columns), and (3) failures occurring after 30,000 hours of use (black columns). STAR = Tyco-Mallinckrodt Infant Star ventilator. VIP = Bird VIP ventilator. 6400ST = Bird 6400ST ventilator. 7200ae = Tyco-Mallinckrodt 7200ae ventilator. 8400STi = Bird 8400STi ventilator. * $p < 0.05$ compared to failures in groups 2 and 3. † $p < 0.05$ compared to group 3.

Discussion

The primary findings of this study are:

1. For the 5 studied brands there was no relationship between ventilator reliability and purchase price or maintenance costs.

2. There is a strong but inverse relationship between reliability and a studied ventilator's age and product age; that is, on average, the older a ventilator is and the longer it has been commercially available, the greater its time before failure.

3. In this study, the site of use (the environment in which the ventilator was operated) played an important role in determining the time before failure.

4. These particular ventilators were just as safe and reliable, regardless of how many times they had previously failed.

Some of the findings in this study were unexpected and contrary to conventional thinking. For instance, while many of us are enticed by items "on sale," collectively, most of us still tend to believe that, as a rule, quality and reliability are a direct function of the purchase price. Clearly, the ventilators in this study did not adhere to that axiom. It is also interesting to note that the prices paid for long-term, preventive maintenance did not influence reliability. Thus, if these ventilators are representative, buying the most expensive ventilators or paying more for preventive maintenance does not confer any quantifiable advantage in terms of safety and reliability.

Another common tenet often applied to ventilators is the belief that most mechanical devices experience failures on an ever-increasing basis as they are used and age.[4] For example, most of us believe that, compared to a new car, one with 100,000 miles on the odometer will have more frequent breakdowns. Figure 3 illustrates the failure rate of the studied ventilators as they were used and aged, depicting the average time before failure versus total hours of ventilator use. When this graph is compared to the concept of an increasing failure rate with age and use, these data present a very different picture. Clearly, for the first 40,000 hours of use or 8 years of use (average use/ventilator/year was approximately 5,000 h; see Table 2), these ventilators became *increasingly* reliable. However, as the superimposed, best-fit polynomial model shows (see Fig. 3), after accumulating over 40,000 hours of use (8 yr), average ventilator reliability seems to have reached a peak. Nevertheless, although reliability deteriorates somewhat beyond 40,000 hours of use, it is still vastly superior to that of a "new" ventilator; this statement is underscored by simply comparing the average reliability of the ventilators with more than 70,000 hours of use to that of relatively new ones (with less than 10,000 hours of operation). Unfortunately, while this information affords us an understanding of how ventilator reliability may change over

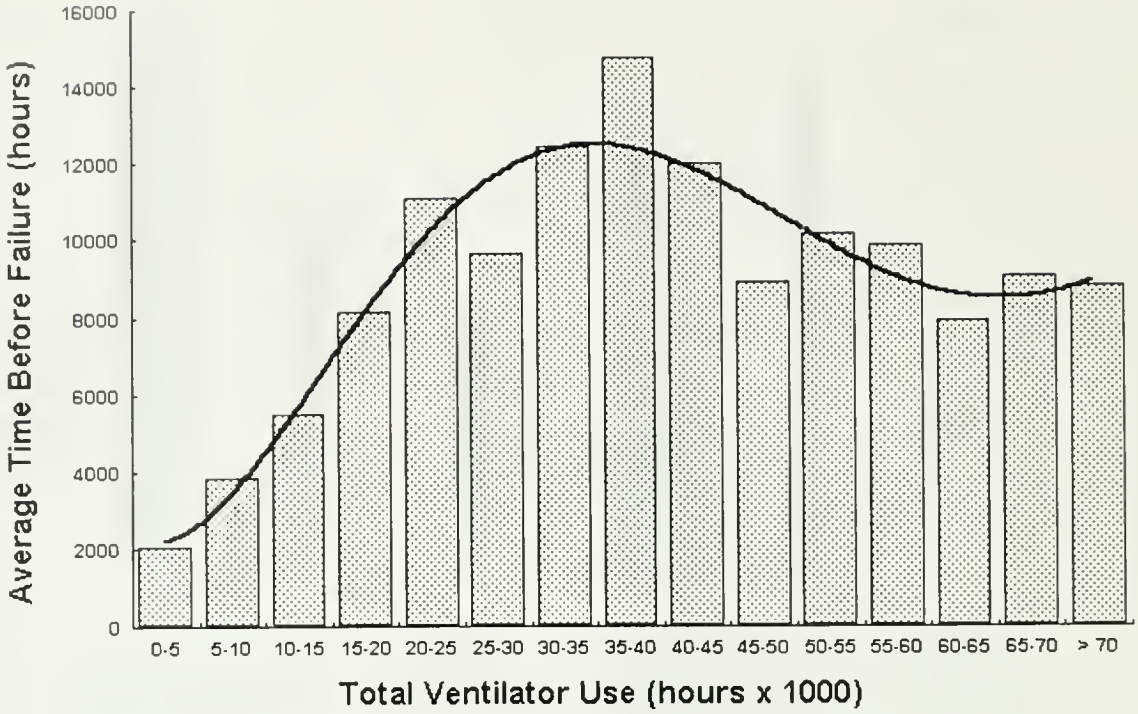


Fig. 3. Average time before failure for 66 mechanical ventilators plotted against total ventilator use. Failure data were subdivided into 15 increments, starting with the failures occurring between 0 and 5,000 hours of use; each successive increment represents the failures that occurred during the next 5,000 hours of ventilator use, except for the final increment, which represents all failures occurring after 70,000 hours of ventilator use. Use for this group of ventilators averaged approximately 5,000 hours/ventilator/year. Superimposed is the best-fit polynomial equation, fitted using the least squares technique.

time, it does not answer the question of how long ventilators can be used safely. However, the information does represent good news for cost-conscious hospital administrators, specifically those hoping to limit capital expenditures by not purchasing new ventilators every 10 years. In fact, in today's cost-conscious health care environment, the common practice of periodically "trading in" ventilators simply because they are "old" might constitute a form of fiscal irresponsibility. Based on these data, it is not an unreasonable approach to continue to repair, maintain, and use mechanical ventilators until they are no longer cosmetically acceptable or until they fail to provide clinicians with the necessary alarms or modes required by the hospital's standard of respiratory care.

It is the goal of any multiple regression analysis to state whether any of the studied covariates correlate with the dependent variable; however, without a way to quantify the effect of any significant covariate(s), the knowledge is of limited practical value. The standard Cox model is particularly useful because it not only determines which covariates are significantly related to survival, but can also be used to graphically display the effect on survival produced by any conceivable level (or combination of levels) of studied covariates. A series of such graphs depicting the effects of ventilator age and product age on time before failure are now examined.

When new products are introduced, the phrase "learning curve" is often heard. The implication is that at the time new products are first released for sale, manufacturers possess very little data concerning the product's long-term reliability. As customers begin to use these products, however, they may begin to experience failures—often too soon. If any particular components appear to be failing too frequently (especially during the warranty period), ethical manufacturers make an effort to replace the faulty component (or components) with a more reliable one. Recalls in the automobile industry represent one example of this process. Product age was included in this analysis to assess whether this process plays an important role in ventilator reliability. In this regard, these data are clear that, on average, the longer a specific brand of ventilator has been on the market the more reliable it becomes (Fig. 4). A possible explanation for this finding is that manufacturers ensure that during repair or periodic overhaul, components recognized as prematurely failing are exchanged for more reliable ones. Some manufacturers freely acknowledge this process and state that their ventilators will become more reliable with age.[10] This process also helps to explain why,

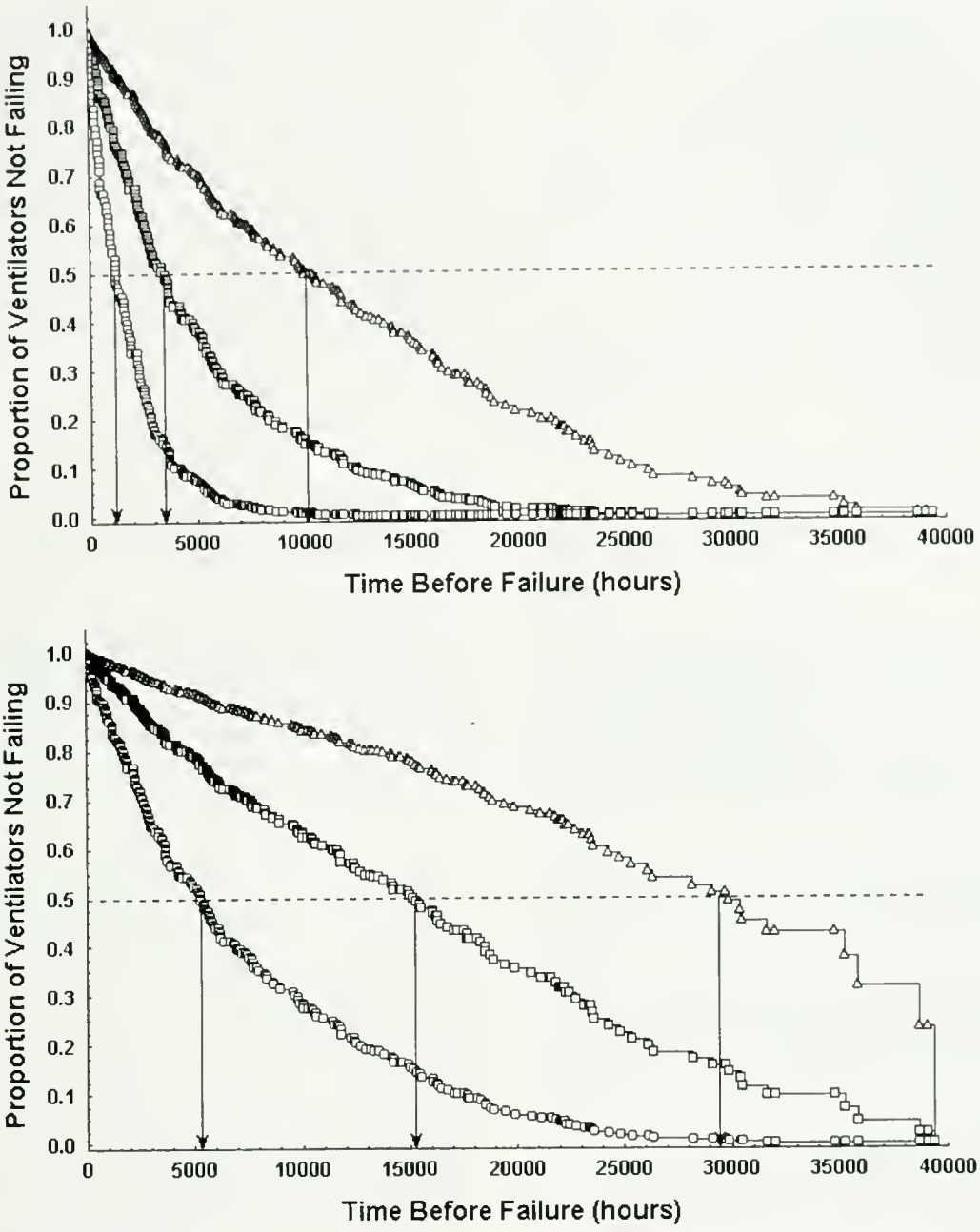


Fig. 4. Two graphs showing the effect on the time before failure made by purchasing ventilators when they are first released for sale compared to waiting several years before purchasing. In each instance the Cox proportional hazard model combined with user-specified values for explanatory covariates were used to graph the predicted time before failure, based on failure data gathered from 66 ventilators used over a period of 9.5 years. The upper panel shows the reliability of a group of the studied ventilators *if* they were purchased when each brand of ventilator was first released for commercial sale. The lower panel shows the reliability of another group of these ventilators *if* they were purchased 10 years after first being released for commercial sale. Each subplot, on both graphs, represents an expected ventilator reliability given a particular set of covariates. In each subplot all explanatory covariates except chronological age and product age were set to the mean values obtained during the study (see Table 3). The dashed horizontal lines demarcate the point at which half of the ventilators have failed. The solid vertical arrows point to the expected hours of use before failure for each subplot. In the upper panel, when the ventilators are new (circles bottom line), both the chronological age and product age are zero. After 5 years of use (squares, middle line), both chronological and product age have increased to 5 years. After 10 years of use (triangles top line), chronological and product age have increased to 10 years. In the lower panel, when the ventilators are new (circles, bottom line), the chronological age is zero but the product age is 10 years. After 5 years of use (squares middle line), chronological age and product age have increased to 5 and 15 years, respectively. When the ventilators have been used for 10 years (triangles, top line), chronological and product age have increased to 10 and 20 years, respectively.

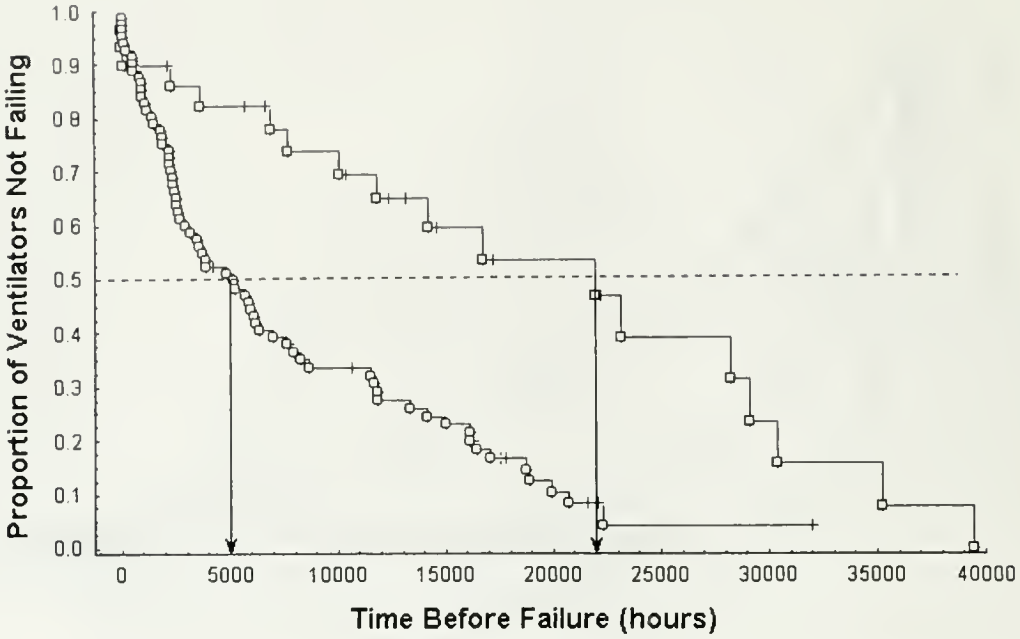


Fig. 5. Time before ventilator failure plotted against the cumulative proportion of ventilators not failing for 2 different groups of ventilators. The dashed horizontal line demarcates the point at which half of the ventilators in either group have failed. The vertical arrows point to the expected hours of use when 50% of the ventilators have failed. The first group (circles, bottom line) comprised 9 Bird 6400ST and 7 Bird 8400STi ventilators used only at a teaching hospital. The second group (squares, top line) comprised 3 Bird 6400ST and 9 Bird 8400STi ventilators used only at a community hospital. The time before failure (survival, top line) was significantly different between the groups ($p < 0.0003$). Censored observations (solid crosses) are represented in each plot.

as a group, these ventilators were safe and reliable regardless of how many times they were previously repaired. Ironically, if we (the consumers) *act* on such information, it would defeat the entire process and create a conundrum. If *everyone* waited for several years before buying a newly released ventilator brand or model, companies would receive no feedback regarding defects and corrective action would be delayed. This would slow product development and greatly impact innovative manufacturers. It would also make products more expensive.

As mentioned, the predictor variables brand and use were judged time-dependent. This finding suggests that some or all of the ventilator brands must exhibit a time before failure that changes as a function of time (use). A breakdown and comparison of the failures by brand, during specific use intervals (see Fig. 2), clearly confirms this hypothesis. For the STAR, VIP, and 6400ST the time before failure was significantly improved at each level of use evaluated. The 8400STi improved so much from the first to second level that the third level was not different from the second. Only the 7200ae showed no significant change in reliability, but there is a plausible explanation for this. Of the 5 studied brands, the 7200ae was the oldest as a product; at completion of the study the 7200ae had been a product for nearly 18 years, compared to 12 years for the STAR and 6400ST and 10 years for the VIP and 8400STi. Possibly, after so many years, engineers at Tyco-Mallinckrodt were asked to focus their attention on developing a new model ventilator (the 840?) or were unable to discover additional improvements that impacted the 7200ae's failure rate.

The average time before unexpected failure for a group of ventilators represents information with many practical uses. For example, consider a facility that uses each of its ventilators an average of 5,000 hours per year and that has a mean time before failure of 9,500 hours. In this hypothetical hospital, each ventilator fails, statistically speaking, approximately once for every 2 years of use. Furthermore, if the average repair costs approximately $1,000,[4] then repairs average approximately $500/ventilator/year. Based on this scenario, a service contract offered at $1,000/ventilator/year[4] no longer seems reasonable. Remember, a service contract should save you money—ostensibly by reducing unexpected repair costs—yet this conjectural respiratory care department would save nearly $500/ventilator/year, by simply foregoing service contracts. Possibly managers purchase these contracts only because they believe ventilators tend to fail more frequently as they age. Based on the performance of the ventilators we studied, however, service contracts represent an insurance policy in reverse: each year you pay the same or higher premiums, yet each year the insured ventilators require fewer repairs.

Another surprising finding was that ventilators used at a community hospital were more reliable than those used at a nearby teaching hospital. This relationship was highly significant when all ventilators were compared and also when only ventilators of the same brand were compared (see Fig. 5). Unfortunately, the study design did not allow me to isolate which factors played the most important role in this finding; nevertheless, such information could eventually provide a mechanism for saving considerable sums of money by replicating the conditions that contributed to the significantly better ventilator reliability at the community hospital.

It is important to note that the 66 ventilators included in this study represent, by definition, a convenience sample. Numbers and variance always strengthen data used for performing regression analysis, so there is little doubt that combining these data with additional data gathered elsewhere would fortify our understanding of ventilator behavior in general.

It is difficult to compare or contrast these data; there are few other scientific studies assessing ventilator reliability. In a related study, I reported significant differences in *average* reliability between the 5 studied brands and speculated that reliability might be improving as a function of time.[7] This study investigates both of these in much greater depth and adds to our understanding of ventilator reliability. Watson and MacIntyre reported that 60 adult ventilators used at their institution experienced 66 failures over a 2 year period (33 failures/year, approximately 0.55 failure/ventilator/year).[3] If we assume similar ventilator use rates, their experience was similar to that of the present study, which saw 226 failures in a 9.5 year period, or 23.8 failures/year (approximately 0.36 failure/ventilator/year). However, when comparing, keep in mind that the definitions of failure used in the 2 studies might not have been identical. Furthermore, some of our ventilators did not participate throughout the entire study (newly purchased ventilators were enrolled as the study progressed), which means that the number of ventilator failures/year may be even closer than they already appear.

Purchasing and maintaining a fleet of mechanical ventilators is an expensive proposition. How often any specific ventilator brand fails has a direct bearing on the long-term cost of ownership, as well as on patient safety. Unfortunately, ventilator reliability is multifactorial and probably changes as a function of time and use. These data indicate that there are variables worth recording that will assist with clinical and financial decision-making regarding mechanical ventilators. Information garnered by combining these data with other data collected elsewhere could eventually allow administrators and clinicians to reduce the risks associated with ventilatory support while concomitantly conserving precious, and seemingly ever-dwindling, health care dollars.

ACKNOWLEDGMENTS

I would like to thank Drs Robert R Kirby and Nikolaus Gravenstein for their sage and timely advice, comments, and encouragement, which contributed greatly to the development of this manuscript.

REFERENCES

1. Bone RC. Acute respiratory failure. In: Burton GG, Hodgkin JE, Ward JJ, editors. Respiratory care: a guide to clinical practice. 3rd ed. Philadelphia: Lippincott; 1991.
2. MacIntyre NR. Mechanical ventilation: the next 50 years. Respir Care 1998;43(6):490–493.
3. Watson H, MacIntyre NR. Mechanical ventilator failure. In: Fulkerson W, MacIntyre NR, editors. Problems in respiratory care: complications of mechanical ventilation. Vol 4. Philadelphia: Lippincott; 1991:127–135.
4. Kacmarek RM. Introducing new mechanical ventilation technology: the hospital perspective. Respir Care 1995;40(9):947–951.
5. Klein EF Jr, Graves SA. "Hot pot" tracheitis. Chest 1974;65(2):225–226.
6. Hall MW, Peevy KJ. Infant ventilator design: performance during expiratory limb occlusion. Crit Care Med 1983;11(1):26–29.
7. Blanch PB. Mechanical ventilator malfunctions: a descriptive and comparative study of 6 common ventilator brands. Respir Care 1999; 44(10):1183–1192.
8. Kleinbaum DG. Survival analysis: a self-learning text. New York: Springer-Verlag; 1996.
9. Punjabi NM. Analysis of failure time data: an introduction to survival analysis. Respir Care 1999;44(10):1198–1202.
10. Infant Star Service and Repair Instructions. Form No. 9910103; San Diego CA, 1998:p 1-2.

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): Executive Summary

Romain A Pauwels MD PhD, A Sonia Buist MD, Peter MA Calverley MD, Christine R Jenkins MD, and Suzanne S Hurd PhD, on behalf of the GOLD Scientific Committee

Preface
Introduction
Definition and Classification of Severity
Definition
Classification of Severity
Pathogenesis
Pathology
Pathophysiology
Burden of Chronic Obstructive Pulmonary Disease
Epidemiology
Economic and Social Burden of COPD
Risk Factors
Host Factors
Exposures
The Four Components of COPD Management
Introduction
Component 1: Assess and Monitor Disease
Component 2: Reduce Risk Factors
Component 3: Manage Stable COPD
Component 4: Manage Exacerbations
Future Research
Consultant Reviewers
Individuals
Organizations
References *Key words: chronic obstructive pulmonary disease, COPD.* [Respir Care 2001;46(8):798–825]

Preface

Chronic obstructive pulmonary disease (COPD) is a major public health problem. It is the fourth leading cause of

The GOLD Executive Summary first appeared in print in the American Journal of Respiratory and Critical Care Medicine (Am J Respir Crit Care Med 2001;163[5]:1256–1276). The entire report (of which this is just a summary), endorsed by the World Health Organization and the United States National Heart, Lung, and Blood Institute of the National Institutes of Health, can be found at http://www.goldcopd.com.

Romain A Pauwels MD PhD, Chair, is affiliated with Ghent University Hospital, Ghent, Belgium. A Sonia Buist MD is affiliated with Oregon Health Science University, Portland, Oregon. Peter MA Calverley MD is affiliated with University Hospital, Aintree, Liverpool, United Kingdom. Christine R Jenkins MD is affiliated with Concord Hospital, Sydney, New South Wales, Australia. Suzanne S Hurd PhD is the Scientific Director of GOLD, Bethesda, Maryland.

GOLD Scientific Committee: Nicholas R Anthonisen MD, University of

chronic morbidity and mortality in the United States[1] and is projected to rank fifth in 2020 as a worldwide burden of disease according to a study published by the World Bank/World Health Organization (WHO).[2] Yet COPD fails to receive adequate attention from the health care community and government officials. With these concerns in mind, a committed group of scientists encouraged the United States National Heart, Lung, and Blood Institute (NHLBI) and the WHO to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Among GOLD's important objectives are to increase awareness of COPD and to help the thousands of people who suffer from this disease and die prematurely from COPD or its complications.

The first step in the GOLD program was to prepare a consensus Workshop Report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*. The GOLD Expert Panel, a distinguished group of health professionals from the fields of respiratory medicine, epidemiology, socioeconomics, public health, and health education, reviewed existing COPD guidelines as well as new information on pathogenic mechanisms of COPD as they developed a consensus document. Many recommendations will require additional study and evaluation as the GOLD program is implemented.

A major problem is the incomplete information about the causes and prevalence of COPD, especially in developing countries. While cigarette smoking is a major known risk factor, much remains to be learned about other causes of this disease. The GOLD Initiative will bring COPD to the attention of governments, public health officials, health care workers, and the general public, but a concerted effort by all involved in health care will be necessary to control this major public health problem.

I would like to acknowledge the dedicated individuals who prepared the Workshop Report and the effective leadership of the Workshop Chair, Professor Romain Pauwels. It is a privilege for the NHLBI to serve as one of the co-sponsors. We look forward to working with the WHO and all other interested organizations and individuals to meet the goals of the GOLD Initiative.

Development of the Workshop Report was supported through educational grants to the Department of Respiratory Diseases of the Ghent University Hospital, Belgium (WHO Collaborating Center for the Management of Asthma and COPD) from ASTA Medica, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, Byk Gulden, Chiesi, GlaxoSmithKline, Merck, Sharp & Dohme, Mitsubishi-Tokyo, Nikken Chemicals, Novartis, Schering-Plough, Yamanouchi, and Zambon Group.

Claude Lenfant MD
Director, National Heart, Lung, and Blood Institute
Bethesda, Maryland

Introduction

Chronic obstructive pulmonary disease is a major cause of chronic morbidity and mortality throughout the world. COPD is currently the fourth leading cause of death in the world,[3] and further increases in the prevalence and mortality of the disease can be predicted in the coming decades. A unified international effort is required to reverse these trends.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is a collaborative project of the United States NHLBI and WHO. Its goals are to increase awareness of COPD and decrease morbidity and mortality from this disease. GOLD aims to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy, and to encourage a renewed research interest in this extremely prevalent disease.

The GOLD Workshop Report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, presents a COPD management plan with 4 components: (1) assess and monitor disease, (2) reduce risk factors, (3) manage stable COPD, and (4) manage exacerbations. The Workshop Report is based on the best-validated current concepts of COPD pathogenesis and the available evidence on the most appropriate management and prevention strategies. It has been developed by individuals with expertise in COPD research and patient care and extensively reviewed by many experts and scientific societies. Before its release for publication, the Workshop Report

---

Manitoba, Winnipeg, Manitoba, Canada; William C Bailey MD, University of Alabama at Birmingham, Birmingham, Alabama; Peter J Barnes MD, National Heart and Lung Institute, London, United Kingdom; Tim Clark MD, Imperial College, London, United Kingdom; Leonardo M Fabbri MD, University of Modena and Reggio Emilia, Modena, Italy; Yoshinosuke Fukuchi MD, Juntendo University, Tokyo, Japan; Lawrence Grouse MD PhD, University of Washington, Seattle, Washington; James C Hogg MD, St Paul's Hospital, Vancouver, British Columbia, Canada; Dirkje S Postma MD, Academic Hospital Groningen, Groningen, The Netherlands; Klaus F Rabe MD, Leiden University Medical Center, Leiden, The Netherlands; Scott D Ramsey MD PhD, University of Washington, Seattle, Washington; Stephen I Rennard MD, University of Nebraska Medical Center, Omaha, Nebraska; Roberto Rodriguez-Roisin MD, University of Barcelona, Barcelona, Spain; Nikos M Siafakas MD, University of Crete Medical School, Heraklion, Greece; Sean D Sullivan PhD, University of Washington, Seattle, Washington; Wan-Cheng Tan MD, National University Hospital, Singapore; Claude Lenfant, National Heart, Lung, and Blood Institute, Bethesda, Maryland; Nikolai Khaltaev, World Health Organization, Geneva, Switzerland.

Correspondence: Romain A Pauwels MD PhD, Department of Respiratory Diseases, University Hospital, De Pintelaan 185, B9000 Ghent, Belgium. E-mail: romain.pauwels@rug.ac.be.

Table 1. Description of Levels of Evidence

Evidence Category	Sources of Evidence	Definition
A	Randomized controlled trials. Rich body of data.	Evidence is from end points of well-designed randomized controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires a substantial number of studies involving substantial numbers of participants.
B	Randomized controlled trials. Limited body of data.	Evidence is from end points of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of randomized controlled trials, or meta-analysis of randomized controlled trials. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The panel consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

was reviewed by the NHLBI and the WHO. This Executive Summary provides key information about COPD; the full Workshop Report provides more details.

In Section 3, "Four Components of COPD Management," levels of evidence are assigned to statements, where appropriate, using a system developed by the NHLBI (Table 1). Levels of evidence are indicated in parentheses after the relevant statement, eg, "(Evidence A)."

Definition and Classification of Severity

Definition

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator forced expiratory volume in the first second (FEV_1) < 80% of the predicted value in combination with an FEV_1/forced vital capacity (FVC) < 70% confirms the presence of airflow limitation that is not fully reversible. Where spirometry is unavailable, the diagnosis of COPD should be made using all available tools. Clinical symptoms and signs, such as abnormal shortness of breath and increased forced expiratory time, can be used to help with the diagnosis. A low peak flow is consistent with COPD, but has poor specificity because it can be caused by other lung diseases and by poor performance. In the interest of improving the diagnosis of COPD, every effort should be made to provide access to standardized spirometry. Chronic cough and sputum production often precede the development of airflow limitation by many years, although not all individuals with cough and sputum production go on to develop COPD.

Classification of Severity

For educational reasons, a simple classification of disease severity into 4 stages is recommended (Table 2). The management of COPD is largely symptom-driven, and there is only an imperfect relationship between the degree of airflow limitation and the presence of symptoms. The staging, therefore, is a pragmatic approach aimed at practical implementation and should only be regarded as an educational tool and a very general indication of the approach to management. All FEV_1 values refer to post-bronchodilator FEV_1.

Stage 0: At Risk. Characterized by chronic cough and sputum production. Lung function, as measured by spirometry, is still normal.

Stage I: Mild COPD. Characterized by mild airflow limitation ($FEV_1/FVC < 70\%$ but $FEV_1 \geq 80\%$ of predicted) and usually, but not always, by chronic cough and sputum production. At this stage, the individual may not even be aware that his or her lung function is abnormal.

Stage II: Moderate COPD. Characterized by worsening airflow limitation ($30\% \leq FEV_1 < 80\%$ of predicted)

Table 2. Classification of COPD by Severity

Stage	Characteristics
0: At Risk	Normal spirometry Chronic symptoms (cough, sputum production)
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ of predicted With or without chronic symptoms (cough, sputum production)
II: Moderate COPD	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 80\%$ of predicted (IIA: $50\% \leq FEV_1 < 80\%$ of predicted) (IIB: $30\% \leq FEV_1 < 50\%$ of predicted) With or without chronic symptoms (cough, sputum production, dyspnea)
III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ of predicted, or the presence of respiratory failure,* or clinical signs of right heart failure

COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
*Respiratory failure = arterial partial pressure of oxygen < 60 mm Hg, with or without arterial partial pressure of carbon dioxide > 50 mm Hg while breathing air at sea level

and usually the progression of symptoms, with shortness of breath typically developing on exertion. This is the stage at which patients typically seek medical attention because of dyspnea or an exacerbation of their disease. The division into Stages IIA and IIB is based on the fact that exacerbations are especially seen in patients with FEV_1 below 50% of predicted. The presence of repeated exacerbations has an impact on the quality of life of patients and requires appropriate management.

Stage III: Severe COPD. Characterized by severe airflow limitation ($FEV_1 < 30\%$ of predicted) or the presence of respiratory failure or clinical signs of right heart failure. Patients may have severe (Stage III) COPD even if the FEV_1 is $> 30\%$ of predicted, whenever these complications are present. At this stage, quality of life is appreciably impaired and exacerbations may be life-threatening.

Poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis, tuberculosis, or asthma is not included except insofar as these conditions overlap with COPD. In many developing countries both pulmonary tuberculosis and COPD are common. Therefore, in all subjects with symptoms of COPD, a possible diagnosis of tuberculosis should be considered, especially in areas where tuberculosis is known to be prevalent. In countries in which the prevalence of tuberculosis is greatly diminished, the possible diagnosis of this disease is sometimes overlooked.

Pathogenesis

COPD is characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature. Macrophages, T lymphocytes (predominately $CD8^+$), and neutrophils are increased in various parts of the lung. Activated inflammatory cells release a variety of mediators—including leukotriene B4,[4] interleukin 8,[5–7] tumor necrosis factor-α[5,8] and others—capable of damaging lung structures or sustaining neutrophilic inflammation. In addition to inflammation, 2 other processes thought to be important in the pathogenesis of COPD are an imbalance of proteinases and antiproteinases in the lung, and oxidative stress.

Inflammation of the lungs is caused by exposure to inhaled noxious particles and gases. Cigarette smoke can induce inflammation and directly damage the lungs.[9–14] Although fewer data are available, it is likely that other COPD risk factors initiate a similar inflammatory process.[15–19] It is believed that this inflammation can then lead to COPD.

Pathology

Pathologic changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. In the central airways—the trachea, bronchi, and bronchioles > 2–4 mm internal diameter—inflammatory cells infiltrate the surface epithelium.[9,20,21] Enlarged mucus-secreting glands and an increase in the number of goblet cells are associated with mucus hypersecretion. In the peripheral airways—small bronchi and bronchioles that have an internal diameter < 2 mm—chronic inflammation leads to repeated cycles of injury and repair of the airway wall.[22] The repair process results in a structural remodeling of the airway wall, with increas-

ing collagen content and scar tissue formation that narrows the lumen and produces fixed airways obstruction.[23]

Destruction of the lung parenchyma in patients with COPD typically occurs as centrilobular emphysema. This involves dilation and destruction of the respiratory bronchioles.[24] These lesions occur more frequently in the upper lung regions in milder cases, but in advanced disease they may appear diffusely throughout the entire lung and also involve destruction of the pulmonary capillary bed. An imbalance of endogenous proteinases and antiproteinases in the lung, resulting from genetic factors or the action of inflammatory cells and mediators, is thought to be a major mechanism behind emphysematous lung destruction. Oxidative stress, another consequence of inflammation, may also contribute.[25]

Pulmonary vascular changes in COPD are characterized by a thickening of the vessel wall that begins early in the natural history of the disease. Thickening of the intima is the first structural change,[26] followed by an increase in smooth muscle and the infiltration of the vessel wall by inflammatory cells.[27] As COPD worsens, greater amounts of smooth muscle, proteoglycans, and collagen[28] further thicken the vessel wall.

Pathophysiology

Pathologic changes in the lungs lead to corresponding physiologic changes characteristic of the disease, including mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale. They usually develop in this order over the course of the disease. Mucus hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. These symptoms can be present for many years before other symptoms or physiologic abnormalities develop.

Expiratory airflow limitation, best measured through spirometry, is the hallmark physiologic change of COPD and the key to diagnosis of the disease. It is primarily caused by fixed airway obstruction and the consequent increase in airway resistance. Destruction of alveolar attachments, which inhibits the ability of the small airways to maintain patency, plays a smaller role.

In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnia. Pulmonary hypertension, which develops late in the course of COPD (Stage III: Severe COPD), is the major cardiovascular complication of COPD and is associated with the development of cor pulmonale and a poor prognosis.[29] The prevalence and natural history of cor pulmonale in COPD are not yet clear.

Burden of COPD

Epidemiology

Most of the information available on COPD prevalence, morbidity, and mortality comes from developed countries. Even in these countries, accurate epidemiologic data on COPD are difficult and expensive to collect. Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced. The imprecise and variable definitions of COPD have made it hard to quantify the morbidity and mortality of this disease in developed[30] and developing countries. Mortality data also underestimate COPD as a cause of death because the disease is more likely to be cited as a contributory than as an underlying cause of death, or may not be cited at all.[31]

Prevalence. In the *Global Burden of Disease* study conducted under the auspices of the WHO and the World Bank,[2,32] the worldwide prevalence of COPD in 1990 was estimated to be 9.34/1,000 in men and 7.33/1,000 in women. However, these estimates include all ages and underestimate the true prevalence of COPD in older adults. The prevalence of COPD is highest in countries where cigarette smoking has been, or still is, very common, whereas the prevalence is lowest in countries where smoking is less common or total tobacco consumption per individual is low.

Morbidity. The limited data that are available indicate that morbidity due to COPD increases with age and is greater in men than women.[1] COPD is responsible for a substantial part of physician visits, emergency department visits, and hospitalizations.

Mortality. COPD is currently the fourth leading cause of death in the world,[3] and further increases in the prevalence and mortality of the disease can be predicted in the coming decades.[2,32] In the United States, COPD death rates are very low among people younger than 45 years of age but then increase with age, and COPD becomes the fourth or fifth leading cause of death among those over 45.[1]

Economic and Social Burden of COPD

Table 3 provides an understanding of the relative economic burden of COPD in 4 countries with Western styles of medical practice and social or private insurance structures. Similar data from developing countries are not available.

The *Global Burden of Disease* study[2,32] estimated the fraction of mortality and disability attributable to major diseases and injuries, using a composite measure of the burden of each health problem, the disability-adjusted life

Table 3. Four-Country Comparison of COPD Direct and Indirect Costs

Country	Year	Direct Cost (US$ Millions)	Indirect Cost (US$ Millions)	Total (US$ Millions)	Per Capita* (US$)
United Kingdom[33]	1996	778	3,312	4,090	65
The Netherlands[34]	1993	256	N/A†	N/A†	N/A†
Sweden[35]	1991	179	281	460	60
United States[1]	1993	14,700	9,200	23,900	87

COPD = chronic obstructive pulmonary disease
*Per capita valuation based on 1993 population estimates from the United Nations Population Council and expressed in 1993 United States dollars
†N/A = not available, the authors did not provide estimates of indirect costs.

year (the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability). According to projections, COPD will be the fifth leading cause of disability-adjusted life years lost worldwide in 2020 (in 1990 it ranked 12th), behind ischemic heart disease, major depression, traffic accidents, and cerebrovascular disease (Table 4).

Risk Factors

Risk factors for COPD include both host factors and environmental exposures, and the disease usually arises from an interaction between these 2 types of factors. The host factor that is best documented is a hereditary deficiency of α-1 antitrypsin. Other genes involved in the pathogenesis of COPD have not yet been identified. The major environmental factors are tobacco smoke; heavy exposure to occupational dusts and chemicals (vapors, irritants, fumes); and indoor/outdoor air pollution. The role of sex as a risk factor for COPD remains unclear. In the past, most studies showed that COPD prevalence and mortality were greater among men than women.[36–39] More recent studies[1,40] from developed countries show that the prevalence of the disease is almost equal in men and women, which probably reflects changing patterns of tobacco smoking. Some studies have in fact suggested that women are more susceptible to the effects of tobacco smoke than men.[38,41] This is an important question given the increasing rate of smoking among women in both developed and developing countries.

Table 4. Leading Causes of Disability-Adjusted Life Years (DALYs) Lost Worldwide: 1990 and 2020 (Projected)

Disease or Injury	Rank 1990	Percent of Total DALYs	Rank 2020	Percent of Total DALYs
Lower respiratory infections	1	8.2	6	3.1
Diarrheal diseases	2	7.2	9	2.7
Perinatal period conditions	3	6.7	11	2.5
Unipolar major depression	4	3.7	2	5.7
Ischemic heart disease	5	3.4	1	5.9
Cerebrovascular disease	6	2.8	4	4.4
Tuberculosis	7	2.8	7	3.1
Measles	8	2.6	25	1.1
Road traffic accidents	9	2.5	3	5.1
Congenital anomalies	10	2.4	13	2.2
Malaria	11	2.3	19	1.5
COPD	12	2.1	5	4.1
Trachea, bronchus, lung cancer	33	0.6	15	1.8

COPD = chronic obstructive pulmonary disease
(Adapted from References 2 and 32.)

Host Factors

Genes. It is believed that many genetic factors increase (or decrease) a person's risk of developing COPD. The genetic risk factor that is best documented is a rare hereditary deficiency of α-1 antitrypsin.[42–44] Premature and accelerated development of panlobular emphysema and decline in lung function occurs in many smokers and nonsmokers with the severe deficiency, although smoking increases the risk appreciably. Other genes involved in the pathogenesis of COPD have not yet been identified.

Airway Hyperresponsiveness. Asthma and airway hyperresponsiveness, identified as risk factors that contribute to the development of COPD,[45] are complex disorders related to a number of genetic and environmental factors. How they influence the development of COPD is unknown. Airway hyperresponsiveness may also develop after exposure to tobacco smoke or other environmental insults and thus may be a result of smoking-related airways disease.

Lung Growth. Lung growth is related to processes occurring during gestation, birthweight, and exposures during childhood.[46–50] Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD.[51]

Exposures

Tobacco Smoke. Cigarette smokers have a higher prevalence of lung-function abnormalities and respiratory symptoms, a greater annual rate of decline in FEV_1, and a higher death rate from COPD than nonsmokers. Pipe and cigar smokers have higher COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers.[52] Not all smokers develop clinically important COPD, which suggests that genetic factors must modify each individual's risk. Passive exposure to cigarette smoke may also contribute to respiratory symptoms and COPD by increasing the lungs' total burden of inhaled particulates and gases.[36,53,54] Smoking during pregnancy may also pose a risk for the fetus, by affecting lung growth and development in utero and possibly the priming of the immune system.[50,55]

Occupational Dusts and Chemicals. When the exposures are sufficiently intense or prolonged, occupational dusts and chemicals (vapors, irritants, fumes) can cause COPD independently of cigarette smoking and increase the risk of the disease in the presence of concurrent cigarette smoking.[56] Exposure to particulate matter, irritants, organic dusts, and sensitizing agents can cause an increase in airway hyperresponsiveness,[57] especially in airways already damaged by other occupational exposures, cigarette smoke, or asthma.

Outdoor and Indoor Air Pollution. High levels of urban air pollution are harmful to persons with existing heart or lung disease. The role of outdoor air pollution in causing COPD is unclear, but appears to be small when compared with cigarette smoking. Indoor air pollution from biomass fuel, burned for cooking and heating in poorly vented dwellings, has been implicated as a risk factor for the development of COPD.[58–67]

Infections. A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood.[51] However, viral infections may be related to another factor (eg, low birthweight) that itself is related to COPD.

Socioeconomic Status. There is evidence that the risk of developing COPD is inversely related to socioeconomic status.[68] It is not clear, however, whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition, or other factors that are related to socioeconomic status.[67,69]

The Four Components of COPD Management

Introduction

An effective COPD management plan includes 4 components: (1) assess and monitor disease, (2) reduce risk factors, (3) manage stable COPD, and (4) manage exacerbations. The goals of effective COPD management are to:

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

These goals should be reached with a minimum of side effects from treatment, a particular challenge in patients with COPD, in whom comorbidities are common. The extent to which these goals can be realized varies with each individual, and some treatments will produce benefits in more than one area. In selecting a treatment plan, the benefits and risks to the individual and the costs, direct and indirect, to the community must be considered.

Patients should be identified before the end stage of the illness, when disability is substantial. However, the benefits of spirometric screening, of either the general population or smokers, are still unclear. Educating patients and physicians to recognize that cough, sputum production, and especially breathlessness are not trivial symptoms is an essential aspect of the public health care of this disease.

Reduction of therapy once symptom control has been achieved is not normally possible in COPD. Further deterioration of lung function requires the progressive introduction of more treatments, both pharmacologic and nonpharmacologic, to attempt to limit the impact of these changes. Acute exacerbations of signs and symptoms, a hallmark of COPD, impair patients' quality of life and decrease their health status. Appropriate treatment and measures to prevent further exacerbations should be implemented as quickly as possible.

Component 1: Assess and Monitor Disease

Key Points

- Diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of symptoms.
- Patients who have chronic cough and sputum production with a history of exposure to risk factors should be

tested for airflow limitation, even if they do not have dyspnea.

· For the diagnosis and assessment of COPD, spirometry is the gold standard, as it is the most reproducible, standardized, and objective way of measuring airflow limitation. $FEV_1/FVC < 70\%$ and a post-bronchodilator $FEV_1 < 80\%$ of predicted confirms the presence of airflow limitation that is not fully reversible.

· Health care workers involved in the diagnosis and management of patients with COPD should have access to spirometry.

· Measurement of arterial blood gases (ABGs) should be considered in all patients with $FEV_1 < 40\%$ of predicted or clinical signs suggestive of respiratory failure or right heart failure.

Diagnosis. A diagnosis of COPD (Table 5) should be considered in any patient who has cough, sputum production, dyspnea, or a history of exposure to risk factors for the disease. The diagnosis is confirmed by an objective measure of airflow limitation, preferably spirometry.

Assessment of Symptoms. Chronic cough, usually the first symptom of COPD to develop,[70] may initially be intermittent, but later is present every day, often throughout the day, and is seldom entirely nocturnal. In some cases, substantial airflow limitation may develop without the presence of a cough. Small quantities of tenacious sputum are commonly raised by COPD patients after coughing bouts. Dyspnea is the reason most patients seek medical attention and is a major cause of disability and anxiety associated with the disease. As lung function deteriorates, breathlessness becomes more intrusive. Wheezing and chest tightness are relatively nonspecific symptoms and may vary between days and over the course of a single day. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD.

Table 5. Key Indicators for Considering a Diagnosis of COPD*

Chronic cough	Present intermittently or every day Often present throughout the day Seldom only nocturnal
Chronic sputum production	Any pattern of chronic sputum production may indicate COPD
Dyspnea that is	Progressive (worsens over time) Persistent (present every day) Described by the patient as "increased effort to breathe," "heaviness," "air hunger," or "gasping" Worse on exercise Worse during respiratory infections
History of exposure to risk factors, especially	Tobacco smoke Occupational dusts and chemicals Smoke from home cooking and heating fuels

*Consider chronic obstructive pulmonary disease (COPD) and perform spirometry if any of these indicators are present. These indicators are not diagnostic by themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

Medical History. A detailed medical history of a new patient known or thought to have COPD should assess:

- Exposure to risk factors.
- Past medical history, including asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood, and other respiratory diseases.
- Family history of COPD or other chronic respiratory disease.
- Pattern of symptom development.
- History of exacerbations or previous hospitalizations for respiratory disorder.
- Presence of comorbidities, such as heart disease and rheumatic disease, that may also contribute to restriction of activity.
- Appropriateness of current medical treatments.
- Impact of disease on patient's life, including limitation of activity, missed work and economic impact, effect on family routines, and feelings of depression or anxiety.
- Social and family support available to the patient.
- Possibilities for reducing risk factors, especially smoking cessation.

Physical Examination. Though an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are rarely present until substantial impairment of lung function has occurred,[71-72] and their detection has a relatively low sensitivity and specificity.

Measurement of Airflow Limitation. To help identify patients earlier in the course of the disease, spirometry should be performed for patients who have chronic cough and sputum production and a history of exposure to risk factors, even if they do not have dyspnea. Spirometry should measure the maximum volume of air forcibly exhaled from the point of maximum inhalation (FVC) and the volume of air exhaled during the first second of this maneuver (FEV_1), and the ratio of these 2 measurements (FEV_1/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of a post-bronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation that is not fully reversible. The FEV_1/FVC on its own is a more sensitive measure of airflow limitation, and an $FEV_1/FVC < 70\%$ is considered an early sign of airflow limitation in patients whose FEV_1

remains normal (≥ 80% of predicted). This approach to defining airflow limitation is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available.

Assessment of Severity. Assessment of severity (Table 2) is based on the level of symptoms, severity of the spirometric abnormality, and the presence of complications such as respiratory failure and right heart failure.

Additional Investigations. For patients in Stage II: Moderate COPD and beyond, the following additional investigations may be useful.

· *Bronchodilator Reversibility Testing.* Generally performed only once, at the time of diagnosis, this test is useful to help rule out a diagnosis of asthma, to establish a patient's best attainable lung function, to gauge a patient's prognosis, and to guide treatment decisions. However, even patients who do not show a significant FEV_1 response to a short-acting bronchodilator test can benefit symptomatically from long-term bronchodilator treatment.

· *Glucocorticosteroid Reversibility Testing.* The simplest, and potentially safest, way to identify patients most likely to respond to long-term glucocorticosteroid treatment is with a treatment trial of inhaled glucocorticosteroids for 6 weeks to 3 months, using as criteria for glucocorticosteroid reversibility an FEV_1 increase of 200 mL and 15% above baseline.[73,74] The response to glucocorticosteroids should be evaluated with respect to the post-bronchodilator FEV_1 (that is, the effect of treatment with inhaled glucocorticosteroids should be in addition to that of regular treatment with a bronchodilator).

· *Chest Radiograph.* A chest radiograph is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution CT might help in the differential diagnosis. In addition, if a surgical procedure such as bullectomy or lung volume reduction is contemplated, chest CT is helpful.

· *Arterial Blood Gas Measurement.* In advanced COPD, measurement of ABGs is important. This test should be performed in patients with $FEV_1 < 40\%$ of predicted or with clinical signs suggestive of respiratory failure or right heart failure. Clinical signs of respiratory failure include central cyanosis, ankle swelling, and an increase in jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of acute exacerbations. Respiratory failure is indicated by an arterial partial pressure of oxygen (P_{aO_2}) < 60 mm Hg, with or without arterial partial pressure of carbon dioxide (P_{aCO_2}) > 45 mm Hg while breathing air at sea level. Measurement of ABGs should be obtained by arterial puncture; finger or ear oximeters for assessing arterial oxygen saturation (S_{aO_2}) are less reliable.

· *α-1 Antitrypsin Deficiency Screening.* In patients who develop COPD at a young age (< 45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting α-1 antitrypsin deficiency. This could lead to family screening and appropriate counseling.

Differential Diagnosis. A major differential diagnosis is asthma. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiologic testing techniques. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (Table 6).

Ongoing Monitoring and Assessment

Monitor Disease Progression and Development of Complications. COPD is usually a progressive disease, and a patient's lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored for development of complications and to determine when to adjust therapy.

Follow-up visits should include a discussion of new or worsening symptoms. Spirometry should be performed if there is a substantial increase in symptoms or a complication. Measurement of ABGs should be performed in all patients who have an $FEV_1 < 40\%$ of predicted or clinical signs of respiratory failure or right heart failure. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of right heart failure in clinical practice. Measurement of pulmonary arterial pressure is not recommended in clinical practice, as it does not add practical information beyond that obtained from a knowledge of P_{aO_2}.

Monitor Pharmacotherapy and Other Medical Treatment. In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and adverse effects of treatment should be monitored.

Monitor Exacerbation History. Frequency, severity, and likely causes of exacerbations should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be docu-

Table 6. Differential Diagnosis of COPD

Diagnosis	Suggestive Features*
COPD	Onset in mid-life Symptoms slowly progressive Long smoking history Dyspnea during exercise Largely irreversible airflow limitation
Asthma	Onset early in life (often in childhood) Symptoms vary from day to day Symptoms at night/early morning Allergy, rhinitis, or eczema also present Family history of asthma Largely reversible airflow limitation
Congestive heart failure	Fine basilar crackles on auscultation Chest radiograph shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation Chest radiograph and computed tomography show bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages Chest radiograph shows lung infiltrate or nodular lesions Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset in younger age, nonsmokers May have history of rheumatoid arthritis or fume exposure Computed tomography on expiration shows hypodense areas
Diffuse panbronchiolitis	Most patients are male and nonsmokers Almost all have chronic sinusitis Chest radiograph and high-resolution computed tomography show diffuse small centrilobular nodular opacities and hyperinflation

COPD = chronic obstructive pulmonary disease

*These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking), and asthma may develop in adult and even elderly patients.

mented, including the facility, duration of stay, and any use of critical care or intubation.

Monitor Comorbidities. In treating patients with COPD, it is important to consider the presence of concomitant conditions such as bronchial carcinoma, tuberculosis, sleep apnea, and left heart failure. The appropriate diagnostic tools (eg, chest radiograph, electrocardiograph) should be used whenever symptoms (eg, hemoptysis) suggest one of these conditions.

Component 2: Reduce Risk Factors

Key Points

· Reduction of total personal exposure to tobacco smoke, occupational dusts, and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD.

· Smoking cessation is the single most effective—and cost-effective—way to reduce the risk of developing COPD and stop its progression (Evidence A).

· Brief tobacco dependence treatment is effective (Evidence A), and every tobacco user should be offered at least this treatment at every visit to the health care provider.

· Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment (Evidence A).

· Several pharmacotherapies for tobacco dependence are available (Evidence A), and at least one of these medications should be added to counseling if necessary and in the absence of contraindications.

Table 7. Strategies to Help the Patient Willing to Quit Smoking

1. ASK:	Systematically identify all tobacco users at every visit. Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented.
2. ADVISE:	Strongly urge all tobacco users to quit. In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. ASSESS:	Determine willingness to make a quit attempt. Ask every tobacco user if he or she is willing to make a quit attempt at this time (eg, within the next 30 days).
4. ASSIST:	Aid the patient in quitting. Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. ARRANGE:	Schedule follow-up contact, either in person or via telephone.

(Adapted from Reference 78.)

· Progression of many occupationally-induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases (Evidence B).

Smoking Prevention and Cessation. Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel. Legislation to establish smoke-free schools, public facilities, and work environments should be encouraged by government officials, public health workers, and the public. Smoking cessation is the single most effective—and cost-effective—way to reduce the risk of developing COPD and stop its progression. Even a brief, 3-minute period of counseling to urge a smoker to quit can be effective, and at the very least this should be done for every smoker at every visit.[75,76] Health education, public policy, and information dissemination programs are all vital components in a comprehensive cessation effort.

Guidelines for Smoking Cessation. Guidelines for smoking cessation were published by the United States Agency for Health Care Policy and Research in 1996[77] and updated in 2000 by the United States Public Health Service in *Treating Tobacco Use and Dependence: A Clinical Practice Guideline*.[78*]

Smoking Cessation Intervention Process. The Public Health Service Report recommends a 5-step program for intervention (Table 7), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment (Evidence A).[77–81]

Pharmacotherapy. Numerous effective pharmacotherapies for smoking cessation now exist (Evidence A).[78,82,83] Except in the presence of special circumstances, pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Numerous studies indicate that nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates.[78,83] The antidepressants bupropion and nortriptyline have also been shown to increase long-term quit rates, although fewer studies have been conducted with these medications.[78,83] The effectiveness of the antihypertensive drug clonidine is limited by adverse effects.[83] Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers (fewer than 10 cigarettes/d), and pregnant and adolescent smokers.

Occupational Exposures. Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures in either developing or developed countries, many occupationally-induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases.[84] Emphasis should be on primary prevention, which is best achieved by the elimination or reduction of exposures to various substances in the workplace. Secondary prevention, achieved through epidemiologic surveillance and early case detection, is also of great importance.

Indoor/Outdoor Air Pollution. Individuals experience diverse indoor and outdoor environments throughout the day, each of which has its own unique set of air contaminants. Although outdoor and indoor air pollution are generally thought of separately, the concept of total personal exposure may be more relevant for COPD. Reducing the risk from indoor and outdoor air pollution requires a combination of public policy and protective steps taken by individual patients.

The health care provider should consider susceptibility (including family history, exposure to indoor/outdoor pol-

* Reprinted in Respir Care 2000;45(10):1200–1262.

lution) for each individual patient.[85] Those who are at high risk should avoid vigorous exercise outdoors during pollution episodes. If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged. Persons with severe COPD should monitor public announcements of air quality and should stay indoors when air quality is poor. Under most circumstances, health care providers should not suggest respiratory protection as a method for reducing the risks of ambient air pollution. Air cleaners have not been shown to have health benefits, whether directed at pollutants generated by indoor sources or at those brought in with outdoor air.

Component 3: Manage Stable COPD

Key Points

- The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease.
- For patients with COPD, health education can play a role in improving skills, ability to cope with illness, and health status. It is effective in accomplishing certain goals, including smoking cessation (Evidence A).
- None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease (Evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms and complications.
- Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms.
- The principal bronchodilator treatments are β_2 agonist, anticholinergics, theophylline, and a combination of one or more of these drugs (Evidence A).
- Regular treatment with inhaled glucocorticosteroids should only be prescribed for symptomatic patients with COPD who have a documented spirometric response to glucocorticosteroids or for those with $FEV_1 < 50\%$ of predicted and repeated exacerbations requiring treatment with antibiotics or oral glucocorticosteroids (Evidence B).
- Prolonged treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (Evidence A).
- All patients with COPD benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (Evidence A).
- The long-term administration of oxygen (> 15 h/d) to patients with chronic respiratory failure has been shown to increase survival (Evidence A).

Introduction. The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease. The management strategy is based on an individualized assessment of disease severity and response to various therapies. Disease severity is determined by the severity of symptoms and airflow limitation, as well as by other factors, such as the frequency and severity of exacerbations, complications, respiratory failure, comorbidities (eg, cardiovascular disease, sleep-related disorders), and the general health status of the patient. Treatment depends on the patient's educational level and willingness to apply the recommended management, on cultural and local conditions, and on the availability of medications.

Education. Although patient education alone does not improve exercise performance or lung function,[86–89] it can play a role in improving skills, ability to cope with illness, and health status.[90] In addition, patient education is effective in accomplishing certain specific goals, including smoking cessation (Evidence A),[41] initiating discussions about and understanding of advance directives and end-of-life issues (Evidence B),[91] and improving patient responses to acute exacerbations (Evidence B).[92,93]

Education may take place in many settings: consultations with physicians or other health care workers, home care or outreach programs, and comprehensive pulmonary rehabilitation programs. It should be tailored to the needs and environment of the patient, interactive, directed at improving quality of life, simple to follow, practical, and appropriate to the intellectual and social skills of the patient and the caregiver. The topics that seem most appropriate for an education program to cover include: smoking cessation; basic information about COPD and pathophysiology of the disease; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; self-management and decision-making in exacerbations; and advance directives and end-of-life issues.

Pharmacologic Treatment. Pharmacologic therapy (Table 8) is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease (Evidence A).[41,94–97] However, this should not preclude efforts to use medications to control symptoms.

Bronchodilators. Bronchodilator medications are central to the symptomatic management of COPD (Evidence A) (Table 9).[98–101] They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. Dose-response relationships using FEV_1 as the outcome are rela-

Table 8. Therapy at Each Stage of COPD*

Stage	Characteristics	Recommended Treatment	
All		Avoidance of risk factors Influenza vaccination	
0: At-Risk	Chronic symptoms (cough, sputum) Exposure to risk factors Normal spirometry		
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ of predicted With or without symptoms	Short-acting bronchodilator when needed	
II: Moderate COPD	IIA: $FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ of predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response
	IIB: $FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$ of predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ of predicted or presence of respiratory failure or right heart failure	Regular treatment with one or more bronchodilators Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations Treatment of complications Rehabilitation Long-term oxygen therapy if respiratory failure Consider surgical treatments	

COPD = chronic obstructive pulmonary disease
*Patients must be taught how and when to use their treatments, and treatments being prescribed for other conditions should be reviewed. Beta-blocking agents (including eye drop formulations) should be avoided
FEV_1 = forced expiratory volume in the fist second
FVC = forced vital capacity

tively flat in all classes of bronchodilators. Side effects are pharmacologically predictable and dose-dependent. Adverse effects are less likely and resolve more rapidly after treatment withdrawal with inhaled than with oral treatment. When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential.

The classes of bronchodilator drugs commonly used in treating COPD—β_2 agonists, anticholinergics, and methylxanthines—are shown in Table 10. The choice depends on the availability of the medication and the patient's response. All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV_1 (Evidence A).[102–104] Regular treatment with short-acting bronchodilators is cheaper but less convenient than treatment with long-acting bronchodilators. The long-acting, inhaled β_2 agonist salmeterol has been shown to improve health status significantly in doses of 50 μg twice daily (Evidence B).[105] Similar data for short-acting β_2 agonists are not available. Use of inhaled ipratropium (an anticholinergic) 4 times daily also improves health status (Evidence B).[106] Theophylline is effective in COPD, but because of its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

Combining drugs with different mechanisms and durations of action might increase the degree of bronchodilation with equivalent or lesser adverse effects. A combination of a short-acting β_2 agonist and the anticholinergic drug ipratropium in stable COPD produces greater and more sustained improvements in FEV_1 than either alone and does not produce evidence of tachyphylaxis over 90 days of treatment (Evidence A).[107–109] Combination of a β_2 agonist, an anticholinergic, or theophylline may produce additional improvements in lung function[107,110–112] and health status.[104,107,110,113] Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when adverse effects are not a limiting factor. Detailed assessments of this approach have not been carried out.

Increasing the dose of either a β_2 agonist or an anticholinergic, especially when given by a wet nebulizer, appears to provide subjective benefit in acute episodes (Evidence B).[114] Some patients may request regular treatment with high-dose, nebulized bronchodilators,[115] especially if they

Table 9. Bronchodilators in Stable COPD

- Bronchodilator medications are central to symptom management in COPD.
- Inhaled therapy is preferred.
- The choice between β_2 agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and adverse effects.
- Bronchodilators are prescribed on an as-needed basis or on a regular basis to prevent or reduce symptoms.
- Long-acting inhaled bronchodilators are more convenient.
- Combining bronchodilators may improve efficacy and decrease the risk of adverse effects, compared to increasing the dose of a single bronchodilator.

COPD = chronic obstructive pulmonary disease

have experienced subjective benefit from this treatment during an acute exacerbation. Clear scientific evidence for this approach is lacking, but one option is to examine the improvement in mean daily peak expiratory flow recording during 2 weeks of treatment in the home and continue with nebulizer therapy if a significant improvement occurs.[115] In general, nebulized therapy for a stable patient is not appropriate unless it has been shown to be better than conventional dose therapy.

Table 10. Commonly Used Bronchodilator Drugs

Drug*	MDI (μg)†	Nebulizer (mg)†	Oral (mg)†	Duration of Action (h)
β_2 agonists				
Fenoterol	100–200	0.5–2.0	—	4–6
Salbutamol (albuterol‡)	100–200	2.5–5.0	4	4–6
Terbutaline	250–500	5–10	5	4–6
Formoterol	12–24	—	—	12+
Salmeterol	50–100	—	—	12+
Anticholinergics				
Ipratropium bromide	40–80	0.25–0.5	—	6–8
Oxitropium bromide	200	—	—	7–9
Methylxanthines§				
Aminophylline (SR)	—	—	225–450	Variable, up to 24
Theophylline (SR)	—	—	100–400	Variable, up to 24

MDI = metered dose inhaler
*Not all products are available in all countries.
†Doses. β_2 agonists refer to average dose given up to 4 times daily for short-acting and 2 times daily for long-acting preparations, anticholinergics are usually given 3–4 times daily
‡Albuterol is a North American generic term.
§Methylxanthines require dose titration depending on adverse effects and plasma theophylline levels

Glucocorticosteroids. Prolonged treatment with inhaled glucocorticosteroids does not modify the long-term decline in FEV_1 in patients with COPD.[94–97] Regular treatment with inhaled glucocorticosteroids is only appropriate for symptomatic COPD patients with a documented spirometric response to inhaled glucocorticosteroids (see Component 1) or in those with $FEV_1 < 50\%$ of predicted (Stage IIB: Moderate COPD and Stage III: Severe COPD) and repeated exacerbations requiring treatment with antibiotics or oral glucocorticosteroids (Evidence B).[94–97] The dose-response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known.

The present guidelines recommend a trial of 6 weeks to 3 months with inhaled glucocorticosteroids to identify patients with COPD who may benefit from long-term inhaled glucocorticosteroid therapy. Many existing COPD guidelines recommend the use of a short course (2 weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD.[96,116]

Long-term treatment with oral glucocorticosteroids is not recommended in COPD (Evidence A).[117–119] There is no evidence of long-term benefit from this treatment. Moreover, an adverse effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy,[118,119] which contributes to muscle weakness, decreased functionality, and respiratory failure in patients with advanced COPD.

Other Pharmacologic Treatments

Vaccines. Influenza vaccines can reduce serious illness and death in patients with COPD by approximately 50%.[120] Vaccines containing killed or live, inactivated viruses are recommended,[121] and should be given once (in autumn) or twice (in autumn and winter) each year (Evidence A). A pneumococcal vaccine containing 23 virulent serotypes has been used, but sufficient data to support its general use in COPD patients are lacking (Evidence B).[122–124]

α-1 Antitrypsin Augmentation Therapy. Young patients with severe hereditary α-1 antitrypsin deficiency and established emphysema may be candidates for α-1 antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for COPD that is not related to α-1 antitrypsin deficiency (Evidence C).

Antibiotics. The use of antibiotics, other than in treating infectious exacerbations of COPD and other bacterial infections, is not recommended (Evidence A).[125,126]

Mucolytic (Mucokinetic, Mucoregulator) Agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol). Although a few patients with viscous sputum may benefit from mucolytics,[127,128] the overall benefits seem to be very small. Therefore, the widespread use of these agents cannot be recommended on the basis of the present evidence (Evidence D).

Antioxidant Agents. Antioxidants, in particular *N*-acetylcysteine, have been shown to reduce the frequency of exacerbations and could have a role in the treatment of patients with recurrent exacerbations (Evidence B).[129–132] However, before their routine use can be recommended, the results of ongoing trials will have to be carefully evaluated.

Immunoregulators (Immunostimulators, Immunomodulators). A study using an immunostimulator in COPD showed a decrease in the severity (though not in the frequency) of exacerbations,[133] but these results have not been duplicated. Thus, the regular use of this therapy cannot be recommended based on the present evidence (Evidence B).[134]

Antitussives. Cough, although sometimes a troublesome symptom in COPD, has an important protective role.[135] Thus, the regular use of antitussives is contraindicated in stable COPD (Evidence D).

Vasodilators. In patients with stable COPD, inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance[136,137] and thus is contraindicated.

Respiratory Stimulants. The use of doxapram, a nonspecific respiratory stimulant available as an intravenous formulation, is not recommended in stable COPD (Evidence D). Almitrine bismesylate is not recommended for regular use in stable COPD patients (Evidence B).[138–140]

Narcotics. Narcotics are contraindicated in COPD because of their respiratory depressant effects and potential to worsen hypercapnia. Clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects.[141–145] Codeine and other narcotic analgesics should also be avoided.

Others. Nedocromil, leukotriene modifiers, and alternative healing methods (eg, herbal medicine, acupuncture, homeopathy) have not been adequately tested in COPD patients and thus cannot be recommended at this time.

Nonpharmacologic Treatments

Rehabilitation. The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. To accomplish these goals, pulmonary rehabilitation covers a range of nonpulmonary problems, including exercise deconditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss. Patients with COPD at all stages of disease benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (Evidence A).[146] Data suggest that these benefits can be sustained even after a single pulmonary rehabilitation program.[147–149] Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings.[150–152]

Ideally, pulmonary rehabilitation should involve several types of health professionals. A comprehensive pulmonary rehabilitation program includes exercise training, nutrition counseling, and education. Baseline and outcome assessments of each participant in a pulmonary rehabilitation program should be made to quantify individual gains and target areas for improvement and should include:

- Detailed medical history and physical examination.
- Measurement of spirometry before and after a bronchodilator drug.
- Assessment of exercise capacity.
- Measurement of health status and the impact of breathlessness.
- Assessment of inspiratory and expiratory muscle strength and lower limb strength (eg, quadriceps) in patients who suffer from muscle wasting (optional).

The first 2 assessments are important for establishing entry suitability and baseline status, but are not used in outcome assessment. The last 3 assessments are essential baseline and outcome measures.

Oxygen Therapy. The long-term administration of oxygen (> 15 h/d) to patients with chronic respiratory failure has been shown to increase survival (Evidence A).[126,127,153,154] It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state.[155]

Long-term oxygen therapy is generally introduced in Stage III: Severe COPD for patients who have (1) $P_{aO_2} \leq$ 55 mm Hg or $S_{aO_2} \leq 88\%$, with or without hypercapnia, or (2) P_{aO_2} between 55 and 60 mm Hg or $S_{aO_2} \leq 89\%$, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit > 55%).

The goal of long-term oxygen therapy is to increase baseline P_{aO_2} to at least 60 mm Hg or to produce S_{aO_2} of at least 90%, which will preserve vital organ function by

ensuring adequate delivery of oxygen. A decision about the use of long-term oxygen should be based on the waking P_{aO_2} values. The prescription should always include the source of supplemental oxygen (gas or liquid), the method of delivery, duration of use, and the flow at rest, during exercise, and during sleep.

Ventilatory Support. To date there is no convincing evidence that mechanical ventilatory support has a role in the routine management of stable COPD.

Surgical Treatments

Bullectomy. In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function (Evidence C).[156] A thoracic CT scan, ABG measurement, and comprehensive respiratory function tests are essential before making a decision regarding a patient's suitability for resection of a bulla.

Lung Volume Reduction Surgery. Although there are some encouraging reports (Evidence C), lung volume reduction surgery is still an unproven palliative surgical procedure.[157,158] Several large randomized studies are now underway to investigate the effectiveness and cost of lung volume reduction surgery in comparison to vigorous conventional therapy.[159] Until the results of these studies are known, lung volume reduction surgery cannot be recommended for widespread use.

Lung Transplantation. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (Evidence C).[160–163] Criteria for referral for lung transplantation include $FEV_1 < 35\%$ of predicted, $P_{aO_2} <$ 55–60 mm Hg, $P_{aCO_2} > 50$ mm Hg, and secondary pulmonary hypertension.[164]

Component 4: Manage Exacerbations

Key Points

- Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD.
- The most common causes of exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one third of severe exacerbations cannot be identified (Evidence B).
- Inhaled bronchodilators (particularly inhaled β_2 agonists or anticholinergics), theophylline, and systemic (preferably oral) glucocorticosteroids are effective treatments for acute exacerbations of COPD (Evidence A).
- Patients experiencing COPD exacerbations with clinical signs of airway infection (eg, increased volume and change of color of sputum, or fever) may benefit from antibiotic treatment (Evidence B).
- Noninvasive positive pressure ventilation (NPPV) in acute exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay (Evidence A).

COPD is often associated with acute exacerbations of symptoms.[165–168] The economic and social burden of COPD exacerbations is extremely high. The most common causes of an exacerbation are infection of the tracheobronchial tree[169–173] and air pollution,[174] but the cause of approximately one third of severe exacerbations cannot be identified.[175] The role of bacterial infections, once believed to be the main cause of COPD exacerbations, is controversial.[169–173,176–178] Conditions that may mimic an acute exacerbation include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia.

Diagnosis and Assessment of Severity. Increased breathlessness, the main symptom of an exacerbation, is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, or new radiologic anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does a prior history of chronic sputum production.[173]

The assessment of the severity of an acute exacerbation is based on the patient's medical history before the exacerbation, symptoms, physical examination, lung function tests, ABG measurements, and other laboratory tests. The medical history should cover how long worsening or new symptoms have been present; the frequency and severity of breathlessness and coughing attacks; sputum volume and color; limitation of daily activities; any previous episodes/exacerbations and whether they required hospitalization; and the present treatment regimen. When available, prior measurements of lung function and ABGs are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. In patients with very severe COPD, the most important sign of severe exacerbation is a change in alertness of the patient, and this signals a need for immediate evaluation in the hospital.

Lung Function Tests. Even simple lung function tests can be difficult for a sick patient to perform properly. In general, a peak expiratory flow < 100 L/min or an $FEV_1 < 1.00$ L indicates a severe exacerbation.[179–181]

Assessment of Arterial Blood Gases. In the hospital, measurement of ABGs is essential to assess the severity of an exacerbation. A $P_{aO_2} < 60$ mm Hg or $S_{aO_2} < 90\%$ (when breathing room air) indicates respiratory failure. In addition, $P_{aO_2} < 50$ mm Hg, $P_{aCO_2} > 70$ mm Hg, and pH < 7.30 point toward a life-threatening episode that needs close monitoring or intensive care unit management.[182]

Chest Radiograph and Electrocardiograph. Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. An electrocardiograph aids in the diagnosis of right ventricular hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an acute exacerbation, especially in severe COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing electrocardiographic and radiographic results. Spiral CT scanning and angiography and perhaps specific D-dimer assays are the best tools presently available for diagnosis of pulmonary embolism in patients with COPD, but ventilation-perfusion scanning is of no value. A low systolic blood pressure and an inability to increase P_{aO_2} above 60 mm Hg despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation.

Other Laboratory Tests. The whole blood count may identify polycythemia (hematocrit > 55%) or bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting antibiotic treatment. *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* are the most common bacterial pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Biochemical tests can reveal whether the cause of the exacerbation is an electrolyte disturbance (eg, hyponatremia or hypokalemia), a diabetic crisis, or poor nutrition (low proteins), and may suggest a metabolic acid-base disorder.

Home Management. There is increasing interest in home care for patients with end-stage COPD, although economic studies of home care services have yielded mixed results. A major outstanding issue is when to treat an exacerbation at home and when to hospitalize the patient.

Bronchodilator Therapy. Home management of COPD exacerbations involves increasing the dose or frequency of existing bronchodilator therapy (Evidence A). If not already used, an anticholinergic can be added until the symptoms improve. In more severe cases, high-dose nebulized therapy can be given on an as-needed basis for several days if a suitable nebulizer is available. However, long-term use of nebulizer therapy after an acute episode is not routinely recommended.

Table 11. Indications for Hospital Assessment or Admission for Acute Exacerbations of COPD*

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe background COPD
- Onset of new physical signs (eg, cyanosis, peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Important comorbidities
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

COPD = chronic obstructive pulmonary disease
*Local resources need to be considered.

Glucocorticosteroids. Systemic glucocorticosteroids are beneficial in the management of acute exacerbations of COPD. They shorten recovery time and help to restore lung function more quickly (Evidence A).[183–185] They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is < 50% of predicted. A dose of 40 mg/d prednisolone for 10 days is recommended (Evidence D).

Antibiotics. Antibiotics are only effective when patients with worsening dyspnea and cough also have increased sputum volume and purulence (Evidence B).[168] The choice of agents should reflect local patterns of antibiotic sensitivity among *S pneumoniae*, *H influenzae*, and *M catarrhalis*.

Hospital Management. The risk of dying from an acute exacerbation of COPD is closely related to the develop-

Table 12. Indications for Intensive Care Unit Admission of Patients with Acute Exacerbation of COPD*

- Severe dyspnea that responds inadequately to initial emergency therapy
- Confusion, lethargy, coma
- Persistent or worsening hypoxemia ($P_{aO_2} < 50$ mm Hg) or severe/worsening hypercapnia ($P_{aCO_2} > 70$ mm Hg), or severe/worsening respiratory acidosis (pH < 7.30) despite supplemental oxygen and noninvasive positive-pressure ventilation

COPD = chronic obstructive pulmonary disease
*Local resources need to be considered
P_{aO_2} = arterial partial pressure of oxygen
P_{aCO_2} = arterial partial pressure of carbon dioxide

ment of respiratory acidosis, the presence of important comorbidities, and the need for ventilatory support.[186] Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts at managing such patients entirely in the community have met with only limited success,[187] but returning them to their homes with increased social support and a supervised medical care package after an initial emergency room assessment has been much more successful.[188] However, detailed cost-benefit analyses of these approaches are awaited.

Hospital assessment/admission should be considered for all patients who fit the criteria shown in Table 11. Some patients need immediate admission to an intensive care unit (Table 12). Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment are available to identify and manage acute respiratory failure successfully.

The first actions when a patient reaches the emergency department are to provide controlled oxygen therapy and to determine whether the exacerbation is life-threatening. If so, the patient should be admitted to the intensive care unit immediately. Otherwise, the patient may be managed in the emergency department or the hospital, as detailed in Table 13.

Controlled Oxygen Therapy. Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Adequate levels of oxygenation ($P_{aO_2} > 60$ mm Hg or $S_{aO_2} > 90\%$) are easy to achieve in uncomplicated exacerbations, but carbon dioxide retention can occur insidiously with little change in symptoms. Once oxygen is started, ABGs should be checked 30 minutes later to ensure satisfactory oxygenation without carbon dioxide retention or acidosis. Venturi masks are more accurate sources of controlled oxygen than are nasal prongs but are more likely to be removed by the patient.

Table 13. Management of Severe But Not Life-Threatening Exacerbations of COPD in the Emergency Department or the Hospital*

- Assess severity of symptoms, blood gases, chest radiograph
- Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 min
- Bronchodilators:
  - Increase dose or frequency
  - Combine β_2 agonists and anticholinergics
  - Use spacers or air-driven nebulizers
  - Consider adding intravenous aminophylline, if needed
- Add glucocorticosteroids (oral or intravenous)
- Consider antibiotics if signs of bacterial infection (oral or occasionally intravenous)
- Consider noninvasive mechanical ventilation
- At all times:
  - Monitor fluid balance and nutrition
  - Consider subcutaneous heparin
  - Identify and treat associated conditions (eg, heart failure, arrhythmias)
  - Closely monitor condition of the patient

COPD = chronic obstructive pulmonary disease
*Local resources need to be considered.

Bronchodilator Therapy. Short-acting, inhaled β_2 agonists are usually the preferred bronchodilators for the treatment of acute exacerbations of COPD (Evidence A).[84,126,127] If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is rather controversial.[189,190] Despite its widespread clinical use, the role of aminophylline in the treatment of COPD exacerbations remains controversial. Most studies of aminophylline have demonstrated minor improvements in lung volumes but also worsening of gas exchange and hypoxemia.[191,192] In more severe exacerbations, addition of an oral or intravenous methylxanthine to the treatment can be considered. However, close monitoring of serum theophylline is recommended to avoid the adverse effects of these drugs.[191,193–195]

Glucocorticosteroids. Oral or intravenous glucocorticosteroids are recommended as an addition to bronchodilator therapy (plus eventually antibiotics and oxygen therapy) in the hospital management of acute exacerbations of COPD (Evidence A).[183–185] The exact dose that should be given is not known, but high doses are associated with a substantial risk of adverse effects. Thirty to 40 mg of oral prednisolone daily for 10–14 days is a reasonable compromise between efficacy and safety (Evidence D). Prolonged treatment does not result in a greater efficacy and increases the risk of adverse effects.

Antibiotics. Antibiotics are only effective when patients with worsening dyspnea and cough also have increased sputum volume and purulence.[168] The choice of agents should reflect local patterns of antibiotic sensitivity among *S pneumoniae*, *H influenzae*, and *M catarrhalis*.

Ventilatory Support. The primary objectives of mechanical support in patients with acute exacerbations in Stage III: Severe COPD are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive mechanical ventilation using either negative or positive pressure devices, and invasive (conventional) mechanical ventilation by orotracheal tube, nasotracheal tube, or tracheostomy.

- *Noninvasive Mechanical Ventilation.* Noninvasive positive pressure ventilation has been studied in many uncon-

Table 14. Selection and Exclusion Criteria for NPPV

Selection Criteria (at least two should be present)
· Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
· Moderate to severe acidosis (pH 7.30–7.35) and hypercapnia (P_{aCO_2} 45–60 mm Hg)
· Respiratory frequency > 25 breaths/min
Exclusion Criteria (any may be present)
· Respiratory arrest
· Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
· Somnolence, impaired mental status, uncooperative patient
· High aspiration risk: viscous or copious secretions
· Recent facial or gastroesophageal surgery
· Craniofacial trauma, fixed nasopharyngeal abnormalities
· Extreme obesity

NPPV = noninvasive positive-pressure ventilation
P_{aCO_2} = arterial partial pressure of carbon dioxide
(Adapted from Reference 200.)

trolled and 5 randomized controlled trials in acute respiratory failure.[196] The studies show consistently positive results, with success rates of 80–85%.[197] Taken together they provide evidence that NPPV increases pH, reduces P_{aCO_2}, reduces the severity of breathlessness in the first 4 hours of treatment, and decreases the length of hospital stay (Evidence A). More importantly, mortality—or its surrogate, intubation rate—is reduced by this intervention.[198–201] However, NPPV is not appropriate for all patients, as summarized in Table 14.

· *Invasive (Conventional) Mechanical Ventilation.* Patients who show impending acute respiratory failure and those with life-threatening acid-base status abnormalities or altered mental status despite aggressive pharmacologic therapy are likely to be the best candidates for invasive mechanical ventilation. The indications for initiating mechanical ventilation during exacerbations of COPD are shown in Table 15, the first being the commonest and most important reason. The 3 ventilatory modes most widely used are assisted-control ventilation, and pressure support ventilation alone or in combination with intermittent mandatory ventilation.[202]

Table 15. Indications for Invasive Mechanical Ventilation

· Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
· Respiratory frequency > 35 breaths/min
· Life-threatening hypoxemia (P_{aO_2} < 40 mm Hg or P_{aO_2}/FIO_2 < 200 mm Hg)
· Severe acidosis (pH < 7.25) and hypercapnia (P_{aCO_2} > 60 mm Hg)
· Respiratory arrest
· Somnolence, impaired mental status
· Cardiovascular complications (hypotension, shock, heart failure)
· Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)
· NPPV failure (or exclusion criteria, see Table 14)

P_{aO_2} = arterial partial pressure of oxygen
FIO_2 = fraction of inspired oxygen
NPPV = noninvasive positive-pressure ventilation
P_{aCO_2} = arterial partial pressure of carbon dioxide

The use of invasive ventilation in patients with end-stage COPD is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities. Major hazards include the risk of ventilator-acquired pneumonia (especially when multiresistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation. Contrary to some opinions, mortality among COPD patients with respiratory failure is no greater than mortality among patients ventilated for non-COPD causes. When possible, a clear statement of the patient's own treatment wishes—an advance directive or "living will"—makes these difficult decisions much easier to resolve.

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD, and the best method to wean patients from the ventilator remains a matter of debate.[203,204] Whether pressure support or a T-piece trial is used, weaning is shortened when a clinical protocol is adopted (Evidence A). Noninvasive ventilation has been applied to facilitate the weaning process in COPD patients with acute or chronic respiratory failure.[205] Compared with invasive pressure support ventilation, NPPV during weaning shortened weaning time, reduced the stay in the intensive care unit, decreased the incidence of nosocomial pneumonia, and improved 60-day survival rates.[205] Similar findings have been reported when NPPV is used after extubation for hypercapnic respiratory failure (Evidence C).[206]

Other Measures. Further treatment measures that can be used in the hospital include: fluid administration (accurate monitoring of fluid balance is essential); nutrition (supplementary when the patient is too dyspneic to eat); low-molecular-weight heparin in immobilized, polycythemic, or dehydrated patients, with or without a history of thromboembolic disease; sputum clearance (by stimulating coughing and low-volume forced expirations, as in home management). Manual or mechanical chest percussion and postural drainage may be beneficial in patients producing > 25 mL sputum per day or with lobar atelectasis.

Hospital Discharge and Follow-Up. Insufficient clinical data exist to establish the optimal duration of hospitalization for acute exacerbations of COPD.[166,207,208] Consensus and limited data support the discharge criteria listed in Table 16. Table 17 provides items to include in a fol-

Table 16. Discharge Criteria for Patients with Acute Exacerbations of COPD

- Inhaled bronchodilator therapy is required no more frequently than every 4 h
- Patient, if previously ambulatory, is able to walk across room
- Patient is able to eat and sleep without frequent awakening by dyspnea
- Patient has been clinically stable for 12–24 h
- Arterial blood gases have been stable for 12–24 h
- Patient (or home caregiver) fully understands correct use of medications
- Follow-up and home care arrangements have been completed (eg, visiting nurse, oxygen delivery, meal provisions)
- Patient, family, and physician are confident patient can manage successfully

COPD = chronic obstructive pulmonary disease

low-up assessment 4–6 weeks after discharge from the hospital. Thereafter, follow-up is the same as for stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters.[84]

If hypoxemia developed during the exacerbation, ABGs should be rechecked at discharge and at the follow-up visit. If the patient remains hypoxemic, long-term oxygen therapy should be instituted. Decisions about continuous domiciliary oxygen based on the severity of the acute hypoxemia during an exacerbation are frequently misleading.

The opportunities for prevention of future exacerbations should be reviewed before discharge, with particular attention to future influenza vaccination plans, knowledge of current therapy (including inhaler technique),[209,210] and how to recognize symptoms of exacerbations. Pharmacotherapy known to reduce the number of exacerbations should be considered. Social problems should be discussed and principal caregivers identified if the patient has a substantial persisting disability.

Future Research

A better understanding of molecular and cellular pathogenetic mechanisms of COPD should lead to many new directions for both basic and clinical investigations. Improved methods for early detection, new approaches for interventions through targeted pharmacotherapy, possible means to identify the "susceptible" smoker, and more effective means of managing exacerbations are needed. Some research recommendations are provided below; there are many additional avenues to explore.

1. Until there is a better understanding of the causal mechanisms of COPD, an absolutely rigid definition of COPD, and its relationship to other obstructive airways diseases, will remain controversial. Defining characteristics of COPD should be identified.

2. The stages of COPD and the disease course will vary from one patient to another. The GOLD report describes 4 stages; their clinical utility needs to be evaluated.

3. Surrogate markers of inflammation, possibly derived from sputum (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species, cytokines) that may predict the clinical usefulness of new management and prevention strategies for COPD need to be developed.

4. Information is needed about the cellular and molecular mechanisms of inflammation in stable COPD and in exacerbations. Inflammatory responses in nonsmokers, exsmokers, and smokers with and without COPD should be compared. The mechanisms responsible for the persistence of the inflammatory response in COPD should be investigated. Why inflammation in COPD is poorly responsive to glucocorticosteroids and what treatments other than glucocorticosteroids are effective in suppressing inflammation in COPD are research topics that could lead to new treatment modalities.

5. There is a pressing need to develop drugs that control symptoms and prevent the progression of COPD. Some progress has been made, and there are several classes of drugs that are now in preclinical and clinical development for use in COPD patients.

6. Standardized methods for tracking trends in COPD prevalence, morbidity, and mortality over time need to be developed so that countries can plan for future increases in the need for health care services in view of predicted increases in COPD. This need is especially urgent in developing countries with limited health care resources.

7. Longitudinal studies demonstrating the course of COPD are needed in a variety of populations exposed to various risk factors. Such studies would provide insight into the pathogenesis of COPD, identify additional genetic bases for COPD, and identify how genetic risk factors interact with environmental risk factors in specific patient populations. Factors that determine why some, but not all, smokers develop COPD need to be identified.

Table 17. Follow-Up Assessment 4–6 Weeks after Discharge from Hospital for an Acute Exacerbation of COPD

- Ability to cope in usual environment
- Measurement of FEV_1
- Reassessment of inhaler technique
- Understanding of recommended treatment regimen
- Need for long-term oxygen therapy or home nebulizer (for patients with severe COPD)

COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in the first second

8. Data are needed on the use, cost, and relative distribution of medical and nonmedical resources for COPD, especially in countries where smoking and other risk factors are prevalent. These data are likely to have some impact on health policy and resource allocation decisions. As options for treating COPD grow, more research will be needed to help guide health care providers and health budget managers regarding the most efficient and effective ways of managing this disease. Methods and strategies for implementation of COPD management programs in developing countries will require special attention.

9. While spirometry is recommended to assess and monitor COPD, other measures need to be developed and evaluated in clinical practice. Reproducible and inexpensive exercise-testing methodologies (eg, stair-climbing tests) suitable for use in developing countries need to be evaluated and their use encouraged. Spirometers need to be developed that can ensure economical and accurate performance when a relatively untrained operator administers the test.

10. Because COPD is not fully reversible (with current therapies) and slowly progressive, it will become ever more important to identify early cases as more effective therapies emerge. Consensus on standard methods for detection and definition of early disease needs to be developed. Data to show whether or not screening spirometry is effective in directing management decisions in COPD outcomes are required.

11. Primary prevention of COPD is one of the major objectives of GOLD. Investigations into the most cost-effective ways to reduce the prevalence of tobacco smoking in the general population and more specifically in young people are very much needed. Strategies to prevent people from starting to smoke and methods for smoking cessation require constant evaluation and improvement. Research is required to gauge the impact and reduce the risk from growing air pollution, urbanization, recurrent childhood infections, occupational exposures, and use of local cigarette equivalents. Programs designed to reduce exposure to biomass fuel in countries where this is used for cooking and domestic heating should be explored in an effort to reduce exposure and improve ventilation in the homes.

12. The specific components of effective education for patients with COPD need to be determined. It is not known, for example, whether patients with COPD should be given an individual management plan, or whether these plans are effective in reducing health care costs or improving the outcomes of exacerbations. Developing and evaluating effective tools for physician education concerning prevention, diagnosis, and management of COPD will be important in view of the increasing public health problem presented by COPD.

13. Studies are needed to determine whether education is an essential component of pulmonary rehabilitation. The cost-effectiveness of rehabilitation programs has not been assessed, and there is a need to assess the feasibility, resource utilization, and health outcomes of rehabilitation programs that can be delivered outside the major teaching hospital setting. Criteria for selecting individuals for rehabilitation should be evaluated, along with methods to modify programs to suit the needs of individual patients.

14. Collecting and evaluating data to set levels of severity for COPD exacerbations would stimulate standardization of this outcome measure that is so frequently used in clinical trials. Better data on outcomes of COPD exacerbations would allow physicians to provide better advice to patients on possible outcomes and appropriateness of various types of treatment. Further exploration of the ethical principles of life support and greater insights into the behavioral influences that inhibit discussion of end-of-life issues are needed, along with studies to define the needs of patients with end-stage COPD.

ACKNOWLEDGMENTS

The authors thank Sarah DeWeerdt for editorial assistance.

Consultant Reviewers

Individuals

P Sherwood Burge (United Kingdom)
Moira Chan-Yeung (Hong Kong)
James F Donohue (United States)
Nicholas J Gross (United States)
Helgo Magnussen (Germany)
Donald A Mahler (United States)
Jean-François Muir (France)
Mrigrendra R Pandey (India)
Peter D Pare (Canada)
Thomas L Petty (United States)
Michael Plit (South Africa)
Sri Ram (United States)
Harold H Rea (New Zealand)
Andrea Rossi (Italy)
Maureen P Rutten-van Molken (The Netherlands)
Marina Saetta (Italy)
Raj Singh (India)
Frank E Speizer (United States)
Robert A Stockley (United Kingdom)
Donald P Tashkin (United States)
G Ian Town (New Zealand)
Paul A Vermeire (Belgium)
Gregory R Wagner (United States)
Scott T Weiss (United States)
Emiel FM Wouters (The Netherlands)
Jan Zielinski (Poland)

Organizations

American College of Chest Physicians. Susan K Pingleton
American Thoracic Society. Bartolome R Celli, William J Martin
Austrian Respiratory Society. Friedrich Kummer
Arab Respiratory Society. Salem El Sayed
Thoracic Society of Australia and New Zealand. Alastair Stewart, David McKenzie, Peter A Frith
Australian Lung Foundation. Robert Edwards
Belgian Society of Pneumology. Marc Decramer, Jean-Claude Yernault
British Thoracic Society. Neil B Pride
Canadian Thoracic Society. Louis-Philippe Boulet, Kenneth R Chapman
Chinese Respiratory Society. Nan-Shan Zhong, Yuanjue Zhu
Croatian Respiratory Society. Neven Rakusic, Davor Plavec
Czech Thoracic Society. Stanislav Kos, Jaromir Musil, Vladimir Vondra
European Respiratory Society. Marc Decramer (Belgium)
French Speaking Pneumological Society. Michel Fournier, Thomas Similowski
Hungarian Respiratory Society. Pal Magyar
Japanese Respiratory Society. Yoshinosuke Fukuchi
Latin American Thoracic Society. Juan Figueroa (Argentina), Maria Christina Machado (Brazil), Ilma Paschoal (Brazil), Jose Jardim (Brazil), Gisele Borzone (Chile), Orlando Diaz (Chile), Patricio Gonzales (Chile), Carmen Lisboa (Chile), Rogelio Perez Padilla (Mexico), Jorge Rodriguez De Marco (Uruguay), Maria Victorina Lopez (Uruguay), Roberto Lopez (Uruguay)
Malaysian Thoracic Society. Zin Zainudin
Norwegian Thoracic Society. Amund Gulsvik, Ernst Omenaas
Polish Phthisiopneumonological Society. Michal Pirozynski
Romanian Society of Pulmonary Diseases. Traian Mihaescu, Sabina Antoniu
Singapore Thoracic Society. Alan Ng, Wei Keong
Slovakian Pneumological and Phthisiological Society. Ladislav Chovan
Slovenian Respiratory Society. Stanislav Suskovic
South African Thoracic Society. James Joubert
Spanish Society of Pneumology. Teodoro Montemayor Rubio, Victor Sobradillo
Swedish Society for Chest Physicians. Kjell Larsson, Sven Larsson, Claes-Goran Lofdahl
Swiss Pulmonary Society. Philippe Leuenberger, Erich Russi
Thoracic Society of Thailand. Ploysongsang Youngyudh
Vietnam Asthma-Allergology and Clinical Immunology Association. Nguyen Nang An

REFERENCES

1. National Heart, Lung, and Blood Institute. Morbidity & Mortality Chartbook on cardiovascular, lung, and blood diseases. Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1998. Available from: URL: www.nhlbi.nih.gov/nhlbi/seiin//other/cht-book/htm.
2. Murray CJL, Lopez AD. Evidence-based health policy - lessons from the global burden of disease study. Science 1996;274:740–743.
3. World health report. Geneva. World Health Organization, 2000. Available from: URL: http://www.who.int/whr/2000/en/statistics.htm.
4. Hill AT, Bayley D, Stockley RA. The interrelationship of sputum inflammatory markers in patients with chronic bronchitis. Am J Respir Crit Care Med 1999;160:893–898.
5. Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma. Am J Respir Crit Care Med 1996;153:530–534.
6. Pesci A, Balbi B, Majori M, Cacciani G, Bertacco S, Alciato P, et al. Inflammatory cells and mediators in bronchial lavage of patients with chronic obstructive pulmonary disease. Eur Respir J 1998;12:380–386.
7. Yamamoto C, Yoneda T, Yoshikawa M, Fu A, Tokuyama T, Tsukaguchi K, et al. Airway inflammation in COPD assessed by sputum levels of interleukin-8. Chest 1997;112:505–510.
8. Mueller R, Chanez P, Campbell AM, Bousquet J, Heusser C, Bullock GR. Different cytokine patterns in bronchial biopsies in asthma and chronic bronchitis. Respir Med 1996;90:79–85.
9. Mullen JB, Wright JL, Wiggs BR, Pare PD, Hogg JC. Reassessment of inflammation of airways in chronic bronchitis. BMJ 1985;291:1235–1239.
10. Cosio M, Ghezzo H, Hogg JC, Corbin R, Loveland M, Dosman J, et al. The relations between structural changes in small airways and pulmonary-function tests. N Engl J Med 1978;298:1277–1281.
11. Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 1974;291:755–758.
12. Wright JL, Lawson LM, Pare PD, Wiggs BJ, Kennedy S, Hogg JC. Morphology of peripheral airways in current smokers and ex-smokers. Am Rev Respir Dis 1983;127:474–477.
13. Ollerenshaw SL, Woolcock AJ. Characteristics of the inflammation in biopsies from large airways of subjects with asthma and subjects with chronic airflow limitation. Am Rev Respir Dis 1992;145:922–927.
14. Hunninghake GW, Crystal RG. Cigarette smoking and lung destruction: accumulation of neutrophils in the lungs of cigarette smokers. Am Rev Respir Dis 1983;128:833–838.
15. Li XY, Brown D, Smith S, MacNee W, Donaldson K. Short-term inflammatory responses following intratracheal instillation of fine and ultrafine carbon black in rats. Inhal Toxicol 1999;11:709–731.
16. Monn C, Becker S. Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine (PM2.5) and coarse particles (PM10–2.5) in outdoor and indoor air. Toxicol Appl Pharmacol 1999;155:245–252.
17. Salvi S, Blomberg A, Rudell B, Kelly F, Sandstrom T, Holgate ST, et al. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med 1999;159:702–709.
18. Von Essen SG, O'Neill DP, McGranaghan S, Olenchock SA, Rennard SI. Neutrophilic respiratory tract inflammation and peripheral blood neutrophilia after grain sorghum dust extract challenge. Chest 1995;108:1425–1433.
19. Von Essen SG, Robbins RA, Thompson AB, Ertl RF, Linder J, Rennard SI. Mechanisms of neutrophil recruitment to the lung by

grain dust exposure. Am Rev Respir Dis 1988;138:921–927. (Erratum appears in Am Rev Respir Dis 1989;139:1065.)
20. O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of $CD8^+$ T lymphocytes with FEV_1. Am J Respir Crit Care Med 1997;155:852–857.
21. Saetta M, Di Stefano A, Maestrelli P, Ferraresso A, Drigo R, Potena A, et al. Activated T-lymphocytes and macrophages in bronchial mucosa of subjects with chronic bronchitis. Am Rev Respir Dis 1993;147:301–306.
22. Saetta M, Di Stefano A, Turato G, Facchini FM, Corbino L, Mapp CE, et al. $CD8^+$ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:822–826.
23. Leopold JG, Goeff J. Centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. Thorax 1957;12:219–235.
24. McLean KA. Pathogenesis of pulmonary emphysema. Am J Med 1958;25:62–74
25. Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. Am J Respir Crit Care Med 1997;156:341–357.
26. Wright JL, Lawson L, Pare PD, Hooper RO, Peretz DI, Nelems JM, et al. The structure and function of the pulmonary vasculature in mild chronic obstructive pulmonary disease: the effect of oxygen and exercise. Am Rev Respir Dis 1983;128:702–707.
27. Peinado VI, Barbera JA, Abate P, Ramirez J, Roca J, Santos S, et al. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1605–1611.
28. Riley DJ, Thakker-Varia S, Poiani GJ, Tozzi CA. Vascular remodeling. In: Crystal RG, West JB, Barnes PJ, Weibel ER, editors. The lung: scientific foundations. Philadelphia: Lippincott-Raven; 1977: 1589–1597.
29. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part 2. Am J Respir Crit Care Med 1994; 150:1158–1168.
30. Pride NB, Vermeire P, Allegra L. Diagnostic labels applied to model case histories of chronic airflow obstruction: responses to a questionnaire in 11 North American and Western European countries. Eur Respir J 1989;2:702–709.
31. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993: an analysis using multiple-cause mortality data. Am J Respir Crit Care Med 1997;156: 814–818.
32. Murray CJL, Lopez AD, editors. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge MA: Harvard University Press; 1996.
33. National Health Service Executive. Burden of disease: a discussion document. London: Department of Health; 1996.
34. Rutten-van Molken MP, Postma MJ, Joore MA, Van Genugten ML, Leidl R, Jager JC. Current and future medical costs of asthma and chronic obstructive pulmonary disease in The Netherlands. Respir Med 1999;93:779–787.
35. Jacobson L, Hertzman P, Lofdahl C-G, Skoogh B-E, Lindgren B. The economic impact of asthma and COPD in Sweden 1980 and 1991. Respir Med 2000;94:247–255.
36. Buist AS, Vollmer WM. Smoking and other risk factors. In: Murray JF, Nadel JA, editors. Textbook of respiratory medicine. Philadelphia: WB Saunders; 1994:1259–1287.
37. Thom TJ. International comparisons in COPD mortality. Am Rev Respir Dis 1989;140:S27–S34.
38. Xu X, Weiss ST, Rijcken B, Schouten JP. Smoking, changes in smoking habits, and rate of decline in FEV_1: new insight into gender differences. Eur Respir J 1994;7:1056–1061.
39. Feinleib M, Rosenberg HM, Collins JG, Delozier JE, Pokras R, Chevarley FM. Trends in COPD morbidity and mortality in the United States. Am Rev Respir Dis 1989;140:S9–S18.
40. US Centers for Disease Control and Prevention. Vital and health statistics: current estimates from the National Health Interview Survey. Department of Health and Human Services, Public Health Service; 1995. Publication No:96–1527.
41. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. JAMA 1994;272:1497–1505.
42. Laurell CB, Eriksson S. The electrophoretic alpha-1 globulin pattern of serum in alpha-1 antitrypsin deficiency. Scand J Clin Lab Invest 1963;15:132–140.
43. Hubbard RC, Crystal RG. Antiproteases. In: Crystal RB, West JB, Barnes PJ, Cherniack NS, Weibel ER, editors. The lung: scientific foundations. New York: Raven Press; 1991:1775–1787.
44. McElvaney NG, Crystal RG. Inherited susceptibility of the lung to proteolytic injury. In: Crystal RG, West JB, Weibel ER, Barnes PJ, editors. The lung: scientific foundations. Philadelphia: Lippincott-Raven; 1997:2537–2553.
45. Orie NGM, Sluiter HJ, De Vreis K, Tammerling K, Wikop J. The host factor in bronchitis. In: Orie NGM, Sluiter HG, editors. Bronchitis, an international symposium. Assen, Netherlands: Royal Vangorcum; 1961:43–59.
46. Hagstrom B, Nyberg P, Nilsson PM. Asthma in adult life—is there an association with birth weight? Scand J Prim Health Care 1998; 16:117–120.
47. Svanes C, Omenaas E, Heuch JM, Irgens LM, Gulsvik A. Birth characteristics and asthma symptoms in young adults: results from a population-based cohort study in Norway. Eur Respir J 1998;12: 1366–1370.
48. Todisco T, de Benedictis FM, Iannacci L, Baglioni S, Eslami A, Todisco E, et al. Mild prematurity and respiratory functions. Eur J Pediatr 1993;152:55–58.
49. Stein CE, Kumaran K, Fall CH, Shaheen SO, Osmond C, Barker DJ. Relation of fetal growth to adult lung function in South India. Thorax 1997;52:895–899.
50. Morgan WJ. Maternal smoking and infant lung function: further evidence for an in utero effect. Am J Respir Crit Care Med 1998; 158:689–690.
51. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes: effect of cigarette smoking and respiratory symptoms. Am Rev Respir Dis 1988;138:837–849.
52. US Surgeon General. The health consequences of smoking: chronic obstructive pulmonary disease. Washington DC: US Department of Health and Human Services; 1984. Publication No:84–50205.
53. Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, et al. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 1994;150:1222–1228.
54. Dayal HH, Khuder S, Sharrar R, Trieff N. Passive smoking in obstructive respiratory disease in an industrialized urban population. Environ Res 1994;65:161–171.
55. Holt PG. Immune and inflammatory function in cigarette smokers. Thorax 1987;42:241–249.
56. Kauffmann F, Drouet D, Lellouch J, Brille D. Twelve years spirometric changes among Paris area workers. Int J Epidemiol 1979;8: 201–212.

57. Niewoehner DE. Anatomic and pathophysiological correlations in COPD. In: Baum GL, Crapo JD, Celli BR, Karlinsky JB, editors. Textbook of pulmonary diseases. Philadelphia: Lippincott-Raven; 1998:823–842.
58. Chen JC, Mannino MD. Worldwide epidemiology of chronic obstructive pulmonary disease. Curr Opin Pulm Med 1999;5:93–99.
59. Perez-Padilla R, Regalado J, Vedal S, Pare P, Chapela R, Sansores R, et al. Exposure to biomass smoke and chronic airway disease in Mexican women. Am J Respir Crit Care Med 1996;154:701–706.
60. Dossing M, Khan J, al-Rabiah F. Risk factors for chronic obstructive lung disease in Saudi Arabia. Respiratory Med 1994;88:519–522.
61. Behera D, Jindal SK. Respiratory symptoms in Indian women using domestic cooking fuels. Chest 1991;100:385–388.
62. Amoli K. Bronchopulmonary disease in Iranian housewives chronically exposed to indoor smoke. Eur Respir J 1998;11:659–663.
63. Dennis R, Maldonado D, Norman S, Baena E, Martinez G. Woodsmoke exposure and risk for obstructive airways disease among women. Chest 1996;109:115–119.
64. Pandey MR. Prevalence of chronic bronchitis in a rural community of the Hill Region of Nepal. Thorax 1984;39:331–336.
65. Pandey MR. Domestic smoke pollution and chronic bronchitis in a rural community of the Hill Region of Nepal. Thorax 1984;39:337–339.
66. Samet JM, Marbury M, Spengler J. Health effects and sources of indoor air pollution. Am Rev Respir Dis 1987;136:1486–1508.
67. Tao X, Hong CJ, Yu S, Chen B, Zhu H, Yang M. Priority among air pollution factors for preventing chronic obstructive pulmonary disease in Shanghai. Sci Total Environ 1992;127:57–67.
68. Prescott E, Lange P, Vestbo J. Socioeconomic status, lung function and admission to hospital for COPD: results from the Copenhagen City Heart Study. Eur Respir J 1999;13:1109–1114.
69. Strachan DP. Epidemiology: a British perspective. In: Calverley PMA, Pride NB, editors. Chronic obstructive pulmonary disease. London: Chapman & Hall; 1995:47–67.
70. Georgopoulas D, Anthonisen NR. Symptoms and signs of COPD. In: Cherniack NS, editor. Chronic obstructive pulmonary disease. Toronto: WB Saunders; 1991:357–363.
71. Loveridge B, West P, Kryger MH, Anthonisen NR. Alteration in breathing pattern with progression of chronic obstructive pulmonary disease. Am Rev Respir Dis 1986;134:930–934.
72. Kesten S, Chapman KR. Physician perceptions and management of COPD. Chest 1993;104:254–258.
73. Reis AL. Response to bronchodilators. In: Clausen J, editor. Pulmonary function testing: guidelines and controversies. New York: Academic Press; 1982.
74. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis 1991;144:1202–1218.
75. Wilson DH, Wakefield MA, Steven ID, Rohrsheim RA, Esterman AJ, Graham NM. "Sick of Smoking": evaluation of a targeted minimal smoking cessation intervention in general practice. Med J Aust 1990;152:518–521.
76. Britton J, Knox A. Helping people to stop smoking: the new smoking cessation guidelines. Thorax 1999;54:1–2.
77. Fiore MC, Bailey WC, Cohen SJ. Smoking cessation: information for specialists. Rockville MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and Centers for Disease Control and Prevention; 1996. AHCPR Publication No. 96–0694.
78. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence. JAMA 2000;283:244–254.
79. American Medical Association. Guidelines for the diagnosis and treatment of nicotine dependence: how to help patients stop smoking. Washington DC: American Medical Association; 1994.
80. Glynn TJ, Manley MW. How to help your patients stop smoking: A National Cancer Institute manual for physicians. Bethesda MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute. 1990. NIH Publication No. 90–3064.
81. Glynn TJ, Manley MW, Pechacek TF. Physician-initiated smoking cessation program: the National Cancer Institute trials. Prog Clin Biol Res 1990;339:11–25.
82. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. JAMA 1994;271:1940–197.
83. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. BMJ 2000;321:355–358.
84. The COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52(Suppl 5):S1–S28.
85. Samet J, Utell MJ. Ambient air pollution. In: Rosenstock L, Cullen M, editors. Textbook of occupational and environmental medicine. Philadelphia: WB Saunders; 1994:53–60.
86. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 1995;122:823–832.
87. Janelli LM, Scherer YK, Schmieder LE. Can a pulmonary health teaching program alter patients' ability to cope with COPD? Rehabil Nurs 1991;16:199–202.
88. Ashikaga T, Vacek PM, Lewis SO. Evaluation of a community-based education program for individuals with chronic obstructive pulmonary disease. J Rehabil 1980;46:23–27.
89. Toshima MT, Kaplan RM, Ries AL. Experimental evaluation of rehabilitation in chronic obstructive pulmonary disease: short-term effects on exercise endurance and health status. Health Psychol 1990;9:237–252.
90. Celli BR. Pulmonary rehabilitation in patients with COPD. Am J Respir Crit Care Med 1995;152:861–864.
91. Heffner JE, Fahy B, Hilling L, Barbieri C. Outcomes of advance directive education of pulmonary rehabilitation patients. Am J Respir Crit Care Med 1997;155:1055–1059.
92. Stewart MA. Effective physician-patient communication and health outcomes: a review. CMAJ 1995;152:1423–1433.
93. Clark NM, Nothwehr F, Gong M, Evans D, Maiman LA, Hurwitz ME, et al. Physician-patient partnership in managing chronic illness. Acad Med 1995;70:957–959.
94. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999;340:1948–1953.
95. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353:1819–1823.
96. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297–1303.

97. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000;343:1902–1909.
98. Vathenen AS, Britton JR, Ebden P, Cookson JB, Wharrad HJ, Tattersfield AE. High-dose inhaled albuterol in severe chronic airflow limitation. Am Rev Respir Dis 1988;138:850–855.
99. Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease: a three-center study. Am Rev Respir Dis 1989;139:1188–1191.
100. Chrystyn H, Mulley BA, Peake MD. Dose response relation to oral theophylline in severe chronic obstructive airways disease. BMJ 1988;297:1506–1510.
101. Higgins BG, Powell RM, Cooper S, Tattersfield AE. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. Eur Respir J 1991; 4:415–420.
102. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. Chest 1987;91: 804–807.
103. Ikeda A, Nishimura K, Koyama H, Tsukino M, Mishima M, Izumi T. Dose response study of ipratropium bromide aerosol on maximum exercise performance in stable patients with chronic obstructive pulmonary disease. Thorax 1996;51:48–53.
104. Guyatt GH, Townsend M, Pugsley SO, Keller JL, Short HD, Taylor DW, et al. Bronchodilators in chronic air-flow limitation: effects on airway function, exercise capacity, and quality of life. Am Rev Respir Dis 1987;135:1069–1074.
105. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med 1997;155: 1283–1289.
106. Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 1999;115:957–965.
107. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 1994;105:1411–1419.
108. COMBIVENT Inhalation Solution Study Group. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. Chest 1997;112:1514–1521.
109. Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group. Respiration 1998;65:354–362.
110. Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single centre randomised, double blind, placebo controlled, crossover study. Thorax 1995;50:750–754.
111. Taylor DR, Buick B, Kinney C, Lowry RC, McDevitt DG. The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible air-flow obstruction. Am Rev Respir Dis 1985;131:747–751.
112. van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld ML, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J 2000;15:878–885.
113. Murciano D, Auclair MH, Pariente R, Aubier M. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. N Engl J Med 1989;320:1521–1525.
114. O'Driscoll BR, Kay EA, Taylor RJ, Weatherby H, Chetty MC, Bernstein A. A long-term prospective assessment of home nebulizer treatment. Respir Med 1992;86:317–325.
115. Tashkin DP, Bleecker E, Braun S, Campbell S, DeGraff AC Jr, Hudgel DW, et al. Results of a multicenter study of nebulized inhalant bronchodilator solutions. Am J Med 1996;100:62S–69S.
116. Senderovitz T, Vestbo J, Frandsen J, Maltbaek N, Norgaard M, Nielsen C, et al. Steroid reversibility test followed by inhaled budesonide or placebo in outpatients with stable chronic obstructive pulmonary disease. The Danish Society of Respiratory Medicine. Respir Med 1999;93:715–718.
117. Rice KL, Rubins JB, Lebahn F, Parenti CM, Duane PG, Kuskowski M, et al. Withdrawal of chronic systemic corticosteroids in patients with COPD: a randomized trial. Am J Respir Crit Care Med 2000; 162:174–178.
118. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. Am J Respir Crit Care Med 1994;150:11–16.
119. Decramer M, Stas KJ. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. Am Rev Respir Dis 1992;146:800–802.
120. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 1994;331:778–784.
121. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis 1994;169:68–76.
122. Simberkoff MS, Cross AP, Al-Ibrahim M, Baltch AL, Geiseler PJ, Nadler J, et al. Efficacy of pneumococcal vaccine in high-risk patients: results of a Veterans Administration cooperative study. N Engl J Med 1986;315:1318–1327.
123. Williams JH Jr, Moser KM. Pneumococcal vaccine and patients with chronic lung disease. Ann Intern Med 1986;104:106–109.
124. Davis AL, Aranda CP, Schiffman G, Christianson LC. Pneumococcal infection and immunologic response to pneumococcal vaccine in chronic obstructive pulmonary disease: a pilot study. Chest 1987;92:204–212.
125. Isada CM, Stoller JK. Chronic bronchitis: the role of antibiotics. In: Niederman MS, Sarosi GA, Glassroth J, editors. Respiratory infections: a scientific basis for management. London: WB Saunders; 1994:621–633.
126. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77–S121.
127. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8:1398–1420.
128. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2000; 2. Available from: URL: www.update-software.com or www.updatusa.com.
129. Hansen NC, Skriver A, Brorsen-Riis L, Balslov S, Evald T, Maltbaek N, et al. Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. Respir Med 1994;88:531–535.
130. British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. Thorax 1985;40:832–835.
131. Boman G, Backer U, Larsson S, Melander B, Wahlander L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: re-

port of a trial organized by the Swedish Society for Pulmonary Diseases. Eur J Respir Dis 1983;64:405–415.
132. Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. Eur Respir J 1988;1:351–355.
133. Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. The PARI-IS Study Steering Committee and Research Group. Prevention of Acute Respiratory Infection by an Immunostimulant. Am J Respir Crit Care Med 1997;156:1719–1724.
134. Anthonisen NR. OM-8BV for COPD. Am J Respir Crit Care Med 1997;156:1713–1714.
135. Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, et al. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. Chest 1998;114:133S–181S.
136. Barbera JA, Roger N, Roca J, Rovira I, Higenbottam TW, Rodriguez-Roisin R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. Lancet 1996;347:436–440.
137. Jones AT, Evans TW. NO: COPD and beyond. Thorax 1997; 52(Suppl 3):S16–S21.
138. Bardsley PA, Howard P, DeBacker W, Vermeire P, Mairesse M, Ledent C, et al. Two years treatment with almitrine bismesylate in patients with hypoxic chronic obstructive airways disease. Eur Respir J 1991;4:308–310.
139. Watanabe S, Kanner RE, Cutillo AG, Menlove RL, Bachand RT Jr, Szalkowski MB, et al. Long-term effect of almitrine bismesylate in patients with hypoxemic chronic obstructive pulmonary disease. Am Rev Respir Dis 1989;140:1269–1273.
140. Winkelmann BR, Kullmer TH, Kneissl DG, Trenk D, Kronenberger H. Low-dose almitrine bismesylate in the treatment of hypoxemia due to chronic obstructive pulmonary disease. Chest 1994; 105:1383–1391.
141. Eiser N, Denman WT, West C, Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the "pink puffer" syndrome. Eur Respir J 1991;4:926–931.
142. Young IH, Daviskas E, Keena VA. Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. Thorax 1989;44:387–390.
143. Rice KL, Kronenberg RS, Hedemark LL, Niewoehner DE. Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. Br J Dis Chest 1987;81:287–292.
144. Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. N Engl J Med 1981;305: 1611–1616.
145. Poole PJ, Veale AG, Black PN. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157:1877–1880.
146. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. Am J Respir Crit Care Med 1999;160:1248–1253.
147. Foglio K, Bianchi L, Bruletti G, Battista L, Pagani M, Ambrosino N. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. Eur Respir J 1999;13:125–132.
148. Young P, Dewse M, Fergusson W, Kolbe J. Improvements in outcomes for chronic obstructive pulmonary disease (COPD) attributable to a hospital-based respiratory rehabilitation programme. Aust N Z J Med 1999;29:59–65.
149. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000; 355:362–368. (Erratum appears in Lancet 2000;355:1280.)
150. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. Lancet 1994;344:1394–1397.
151. Wijkstra PJ, Van Altena R, Kraan J, Otten V, Postma DS, Koeter GH. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. Eur Respir J 1994; 7:269–273.
152. McGavin CR, Gupta SP, Lloyd EL, McHardy GJ. Physical rehabilitation for the chronic bronchitic: results of a controlled trial of exercises in the home. Thorax 1977;32:307–311.
153. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980;93:391–398.
154. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981;1:681–686.
155. Tarpy SP, Celli BR. Long-term oxygen therapy. N Engl J Med 1995;333:710–714.
156. Mehran RJ, Deslauriers J. Indications for surgery and patient work-up for bullectomy. Chest Surg Clin N Am 1995;5:717–734.
157. Benditt JO, Albert RK. Surgical options for patients with advanced emphysema. Clin Chest Med 1997;18:577–593.
158. Geddes D, Davies M, Koyama H, Hansell D, Pastorino U, Pepper J, et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. N Engl J Med 2000;343:239–245.
159. The National Emphysema Treatment Trial Research Group. Rationale and design of The National Emphysema Treatment Trial: a prospective randomized trial of lung volume reduction surgery. Chest 1999;116:1750–1761.
160. Trulock EP. Lung transplantation. Am J Respir Crit Care Med 1997;155:789–818.
161. Theodore J, Lewiston N. Lung transplantation comes of age. N Engl J Med 1990;322:772–774.
162. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: fifteenth official report—1998. J Heart Lung Transplant 1998;17:656–668.
163. Annual report of the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network. Transplant data: 1988–1994. Washington DC: Division of Transplantation, Health Resources and Services Administration, US Department of Health and Human Services; 1995.
164. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society. Transplantation 1998;66:951–956.
165. Regueiro CR, Hamel MB, Davis RB, Desbiens N, Connors AF Jr, Phillips RS. A comparison of generalist and pulmonologist care for patients hospitalized with severe chronic obstructive pulmonary disease: resource intensity, hospital costs, and survival. SUPPORT Investigators. Am J Med 1998;105:366–372.
166. Gibson PG, Wlodarczyk JH, Wilson AJ, Sprogis A. Severe exacerbation of chronic obstructive airways disease: health resource use in general practice and hospital. J Qual Clin Pract 1998;18:125–133.

167. Warren PM, Flenley DC, Millar JS, Avery A. Respiratory failure revisited: acute exacerbations of chronic bronchitis between 1961–68 and 1970–76. Lancet 1980;1:467–470.
168. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196–204.
169. Wilson R. The role of infection in COPD. Chest 1998;113:242S–248S.
170. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 1998;157:1498–1505.
171. Smith CB, Kanner RE, Golden CA, Klauber MR, Renzetti AD Jr. Effect of viral infections on pulmonary function in patients with chronic obstructive pulmonary diseases. J Infect Dis 1980;141:271–280.
172. MacFarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. Lancet 1993;341:511–514.
173. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 2000;117:1638–1645.
174. Anderson HR, Spix C, Medina S, Schouten JP, Castellsague J, Rossi G, et al. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. Eur Respir J 1997;10:1064–1071.
175. Chodosh S, McCarty J, Farkas S, Drehobl M, Tosiello R, Shan M, et al. Randomized, double-blind study of ciprofloxacin and cefuroxime axetil for treatment of acute bacterial exacerbations of chronic bronchitis. The Bronchitis Study Group. Clin Infect Dis 1998;27:722–729.
176. Walsh EE, Falsey AR, Hennessey PA. Respiratory syncytial and other virus infections in persons with chronic cardiopulmonary disease. Am J Respir Crit Care Med 1999;160:791–795.
177. Mogulkoc N, Karakurt S, Isalska B, Bayindir U, Celikel T, Korten V, et al. Acute purulent exacerbation of chronic obstructive pulmonary disease and *Chlamydia pneumoniae* infection. Am J Respir Crit Care Med 1999;160:349–353.
178. Murphy TF, Setbi S, Klingman KL, Brueggemann AB, Doern GV. Simultaneous respiratory tract colonization by multiple strains of nontypeable *Haemophilus influenzae* in chronic obstructive pulmonary disease: implications for antibiotic therapy. J Infect Dis 1999;180:404–409.
179. Emerman CL, Effron D, Lukens TW. Spirometric criteria for hospital admission of patients with acute exacerbation of COPD. Chest 1991;99:595–599.
180. Emerman CL, Lukens TW, Effron D. Physician estimation of FEV_1 in acute exacerbation of COPD. Chest 1994;105:1709–1712.
181. Emerman CL, Cydulka RK. Use of peak expiratory flow rate in emergency department evaluation of acute exacerbation of chronic obstructive pulmonary disease. Ann Emerg Med 1996;27:159–163.
182. Emerman CL, Connors AF, Lukens TW, Effron D, May ME. Relationship between arterial blood gases and spirometry in acute exacerbations of chronic obstructive pulmonary disease. Ann Emerg Med 1989;18:523–527.
183. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 1996;154:407–412.
184. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999;354:456–460.
185. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med 1999;340:1941–1947.
186. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators. Am J Respir Crit Care Med 1996;154:959–967.
187. Shepperd S, Harwood D, Gray A, Vessey M, Morgan P. Randomised controlled trial comparing hospital at home care with inpatient hospital care. II: cost minimisation analysis. BMJ 1998;316:1791–1796.
188. Gravil JH, Al-Rawas OA, Cotton MM, Flanigan U, Irwin A, Stevenson RD. Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. Lancet 1998;351:1853–1855.
189. Moayyedi P, Congleton J, Page RL, Pearson SB, Muers MF. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. Thorax 1995;50:834–837.
190. Fernandez A, Munoz J, de la Calle B, Alia I, Ezpeleta A, de la Cal MA, et al. Comparison of one versus two bronchodilators in ventilated COPD patients. Intensive Care Med 1994;20:199–202.
191. Barbera JA, Reyes A, Roca J, Montserrat JM, Wagner PD, Rodriguez-Roisin R. Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbations of chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;145:1328–1333.
192. Mahon JL, Laupacis A, Hodder RV, McKim DA, Paterson NA, Wood TE, et al. Theophylline for irreversible chronic airflow limitation: a randomized study comparing n of 1 trials to standard practice. Chest 1999;115:38–48.
193. Lloberes P, Ramis L, Montserrat JM, Serra J, Campistol J, Picado C, et al. Effect of three different bronchodilators during an exacerbation of chronic obstructive pulmonary disease. Eur Respir J 1988;1:536–539.
194. Murciano D, Aubier M, Lecocguic Y, Pariente R. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. N Engl J Med 1984;311:349–353.
195. Emerman CL, Connors AF, Lukens TW, May ME, Effron D. Theophylline concentrations in patients with acute exacerbation of COPD. Am J Emerg Med 1990;8:289–292.
196. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. Ann Intern Med 1994;120:760–770.
197. International Consensus Conferences in Intensive Care Medicine. Noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 2001;163:283–291.
198. Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993;341:1555–1557.
199. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A,et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995;333:817–822.
200. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 1995;151:1799–1806.
201. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet 2000;355:1931–1935.
202. Esteban A, Anzueto A, Alia I, Gordo F, Apezteguia C, Palizas F, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med 2000;161:1450–1458.

203. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona Jr, Valverdu I, et al, for the Spanish Lung Failure Collaborative Group. A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med 1995;332:345–350.
204. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994;150:896–903.
205. Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: a randomized, controlled trial. Ann Intern Med 1998;128:721–728.
206. Hilbert G, Gruson D, Portel L, Gbikpi-Benissan G, Cardinaud JP. Noninvasive pressure support ventilation in COPD patients with postextubation hypercapnic respiratory insufficiency. Eur Respir J 1998;11:1349–1353.
207. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:158–164.
208. Mushlin AI, Black ER, Connolly CA, Buonaccorso KM, Eberly SW. The necessary length of hospital stay for chronic pulmonary disease. JAMA 1991;266:80–83.
209. Stoller JK, Lange PA. Inpatient management of chronic obstructive pulmonary disease. Respir Care Clin N Am 1998;4:425–438.
210. Peach H, Pathy MS. Follow-up study of disability among elderly patients discharged from hospital with exacerbations of chronic bronchitis. Thorax 1981;36:585–589.

Letters

Letters addressing topics of current interest or material in RESPIRATORY CARE will be considered for publication. The Editors may accept or decline a letter or edit without changing the author's views. The content of letters as published may simply reflect the author's opinion or interpretation of information—not standard practice or the Journal's recommendation. Authors of criticized material will have the opportunity to reply in print. No anonymous letters can be published. Type letter double-spaced, mark it "For Publication," and mail it to RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104. Letters may also be submitted electronically at www.rcjournal.com/online_resources.

High-Frequency Jet Ventilation

I was enjoying the article "Tracheal Gas Insufflation and Related Techniques to Introduce Gas Flow into the Trachea" by Drs Dean Hess and Michael Gillette (Respir Care 2001;46(2):119–129), until I got to the section on high-frequency jet ventilation (HFJV). It was loaded with misinformation, such as their estimates that HFJV tidal volumes are 3–5 mL/Kg. Several investigators have demonstrated that high-frequency ventilation (HFV) devices of various designs produce normal gas exchange using tidal volumes smaller than the anatomic dead space of the lungs (2 mL/Kg).[1–5] (These studies were conducted in the 1970s, using normal rabbits and dogs and dogs with diffuse lung injury.)

There are many reasons why HFJV has been virtually abandoned in adult intensive care units, but assuming it is because HFJV doesn't work isn't one of them. Like tracheal gas insufflation (TGI), HFJV is a therapy that does not mimic natural breathing. HFJV is a therapy that requires well-designed equipment, a company to manufacture and service that equipment, and clinicians with the training and discipline to master its application.

The next article in that (February 2001) issue of RESPIRATORY CARE, also by Drs Hess and Gillette, "Ventilator-Induced Lung Injury and the Evolution of Lung-Protective Strategies in Acute Respiratory Distress Syndrome" (Respir Care 2001; 46(2):130–148), similarly dismissed high-frequency oscillation (HFO). Why are these authors so negative towards techniques that avoid overdistending the lungs through the use of very small tidal volumes while ventilating very effectively? (HFV operators more often have problems getting partial pressure of carbon dioxide *up* to normal, rather than worrying about permissively hypoventilating.)

Several HFV reports cited by Drs Hess and Gillette have been superseded by improvements in equipment or ventilator strategy. The progression of positive studies in neonatology that define our ever-improving HFV knowledge were neglected in Hess and Gillette's reviews. It takes time to learn how to optimize any new therapy, and HFV therapy, unlike all other ventilator therapies, has developed under very strict Class III Food and Drug Administration regulations. These regulations, while undoubtedly improving safety, have prolonged the validation process.

HFJV and HFO have been shown to be protective of proper lung development in prematurely delivered animals and animal models of adult acute respiratory distress syndrome (ARDS). Early HFO studies in premature baboons by Meredith et al[6] and Gerstmann et al[7] are classics in our field. More recent HFJV studies with premature lambs have been presented at various meetings, but have yet to be published.[8]

HFJV studies indicate less lung injury and more normal pulmonary alveolar and circulatory development than either small tidal volume with rapid rate (5 mL/Kg, 60 cycles/min) or large tidal volume with slow rate (15 mL/Kg, 20 cycles/min) intermittent mandatory ventilation. Animals ventilated right from birth with 1–2 mL/Kg HFJV tidal volumes at 420 cycles/min were easier to care for and demonstrated better survival, improved alveolar development, more uniform lung inflation, less atelectasis, and less smooth muscle in small arteries and airways. However, there was no benefit on lung elastin accumulation or edema, and no benefit on lung pathophysiology.[8]

Not all the studies produced positive results, as Hess and Gillette most adequately indicated. The randomized clinical trial of HFJV in adults conducted in the early 1980s was disappointing. So was the first HFO study in infants (the "HIFI study").[9] However, we learned a great deal from these and other "negative" studies.

More recent HFJV and HFO randomized clinical trials have shown significant reductions in chronic lung disease when applied early for the treatment of ARDS in neonates.[10,11] HFJV has also demonstrated success with treating pulmonary interstitial emphysema,[12] arguably the most deadly lung injury afflicting mechanically ventilated premature infants.

Few neonatologists would argue that HFV hasn't improved mortality rates, despite the fact that our studies are seldom designed with death as an end point. While hard science may be compromised, crossovers to the alternately assigned mode of therapy or rescue by extracorporeal membrane oxygenation are the norm in studies with critically ill infants. When mortality rates by originally assigned group are "corrected" by crediting survival to the rescue therapy afforded by crossovers, HFV has led to statistically higher survival rates.[11,12] A study of persistent pulmonary hypertension of the newborn showed a survival rate of 45% —without extracorporeal membrane oxygenation—for the infants randomized to HFJV, versus 23% for those treated conventionally.[13]

Our greatest challenge with HFV has been learning how to use it optimally. Using HFV incorrectly, just like any other therapy, can lead to increased adverse effects. For example, some studies of HFV have raised concern over an increased incidence of severe neuro-imaging abnormalities such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL).[9,14]

Clark et al conducted a meta-analysis to determine if premature neonates treated with HFV are at greater risk of developing IVH or PVL than are infants treated with conventional ventilation.[15] They found that there was an association between the use of HFV and PVL, but not IVH. However, the HIFI study was much larger than all the other studies,[9] and it was conducted before there was widespread appreciation of the importance of maintaining optimal lung volume during HFV. When the HIFI study was removed from the analysis, the association between HFV and PVL disappeared.

In randomized clinical trials where HFJV was compared to conventional ventilation for the treatment of ARDS in premature infants, severe IVH and PVL increased when positive end-expiratory pressure (PEEP) was kept too low (ie, 5 cm H_2O).[9,14] Low PEEP was associated with lower arterial partial pressure of oxygen and hypocarbia in affected patients. Speculation held that low PEEP during HFJV leads to hyperventilation, because peak inspiratory pressure is kept unnecessarily high in order to maintain

adequate mean airway pressure for oxygenation. When higher PEEP was used to maintain appropriate lung volume, arterial partial pressure of oxygen values were higher and arterial partial pressure of carbon dioxide values were more normal.[11] Severe IVH or PVL incidence in the infants treated with HFJV and higher PEEP (8.8%) was statistically lower than that of the conventionally ventilated control group (28%) or a subgroup of infants treated with HFJV and lower PEEP (33%).

Some of us view TGI as an extreme form of HFJV. If one raises HFJV to the highest imaginable frequency, one reaches constantly injected gas flow (one form of TGI). If one takes TGI and chops the gas flow into little pieces (aka, tidal volumes), one gets HFJV. There are pros and cons to each approach, but both try to capitalize on the same fluid mechanical and gas exchange phenomena whilst attempting to minimize lung injury. Both techniques require proper humidification to avoid damaging tracheobronchial mucosa. Neither approach requires a closed system.

To discount HFV is to discount the thousands of clinicians who use this technology to save thousands of pediatric patients each year, most of whom have failed every available conventional ventilation technique.

J Bert Bunnell ScD
Bunnell Inc
Salt Lake City, Utah

REFERENCES

1. Lunkenheimer PP, Rafflenbeul W, Keller H, Frank I, Dickhurt HH, Fuhrmann C. Application of transtracheal pressure oscillations as a modification of "diffusion respiration." Br J Anaesth 1972;44(6):627.
2. Bunnell JB, Karlson KH, Shannon DC. High frequency positive pressure ventilation in dogs and rabbits. Am Rev Respir Dis 1978;117(Suppl):289a.
3. Custer JR, Shannon DC. High frequency ventilation enhances oxygenation and alveolar ventilation at reduced airway pressures in animal model of pulmonary edema. Am Rev Respir Dis 1979;119(Suppl):226a.
4. Bohn DJ, Miyasaka K, Marchak BE, Thompson WK, Froese AB, Bryan AC. Ventilation by high frequency oscillation. J Appl Physiol 1980;48(4):710–716.
5. Slutsky AS, Drazen JM, Ingram RH Jr, Kamm RD, Shapiro AH, Fredberg JJ, et al. Effective pulmonary ventilation with small-volume oscillations at high frequencies. Science 1980;209(4456):609–671.
6. Meredith KS, deLemos RA, Coalson JJ, King RJ, Gerstmann DR, Kumar R, et al. Role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. J Appl Physiol 1989;66(5):2150–2158.
7. Gerstmann DR, deLemos RA, Clark RH. High frequency ventilation: issues of strategy. Clin Perinatol 1991;18(3):563–580.
8. Albertine KH, Jones GP, Stolworthy LD, et al. High-frequency jet ventilation lessens the severity of lung injury in chronically ventilated preterm lambs. 15th Conf. on High Frequency Ventilation of Infants and Children, Apr 1, 1998, Snowbird, Utah.
9. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. HIFI Study Group. New Engl J Med 1989;320(2):88–93.
10. Gerstmann DR, Minton SD, Stoddard RA, Meredith KS, Monaco F, Bertrand JM, et al. The Provo multicenter early High-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 1996;98(6 Pt 1:1044–1057.
11. Keszler M, Modanlou HD, Brudno DS, Clark FI, Cohen RS, Ryan RM, et al. Multicenter controlled clinical trial of High-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics 1997;100(4):593–599.
12. Keszler M, Donn SM, Bucciarelli RL, Alverson DC, Hart M, Lunyong V, et al. Multicenter controlled trial comparing High-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr 1991;119(1 Pt 1):85–93.
13. Engle WA, Yoder MC, Andreoli SP, Darragh RK, Langefeld CD, Hui SL. Controlled prospective randomized comparison of High-frequency jet ventilation and conventional ventilation in neonates with respiratory failure and persistent pulmonary hypertension. J Perinatol 1997;17(1):3–9.
14. Wiswell TE, Graziani LJ, Kornhauser MS, Cullen J, Merton DA, McKee L, Spitzer AR. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. Pediatrics 1996;98(6 Pt 1):1035–1043.
15. Clark RH, Dykes FD, Bachman TE, Ashurst JT. Intraventricular hemorrhage and High-frequency ventilation: a meta-analysis of prospective clinical trials. Pediatrics 1996; 98(6 Pt 1):1058–1061.

The author replies:

Dr Bunnell raises concerns about our papers,[1,2] in which he believes we shed a negative light on HFV.

First of all, the reader should understand that the focus of the papers by Dr Gillette and me are related to ARDS in adults. HFV has an indisputable role in neonates, and it has indeed improved outcomes in that patient population. We do not debate the value of HFV in neonates—but that was not the topic of our papers!

Considerable caution must be exercised when extrapolating from animal studies to humans. Animal studies are invaluable to demonstrate proof-of-concept. However, the results of animal studies must be confirmed in humans before acceptance into patient care. The literature is replete with examples of drugs and techniques that seemed promising in animal models, only to fail in human studies. Demonstrating that normal gas exchange can occur in a small animal model using HFV does not mean that the same will occur in an adult with ARDS. Moreover, as we state in our paper,[1] with high-frequency jet ventilation, the high velocity at which gas exits the jet causes additional gas to be entrained and makes measurement of delivered tidal volume virtually impossible in the clinical setting.

Equal caution must be exercised when extrapolating from one patient population to another. Just because HFV has been shown to benefit neonates with ARDS does not mean that similar results should be expected in adults with ARDS. One only needs to look at inhaled nitric oxide to demonstrate this point. Although inhaled nitric oxide has been shown to benefit newborns with hypoxemic respiratory failure (and the Food and Drug Administration has approved the use of inhaled nitric oxide for this indication), large multicenter randomized trials have not demonstrated benefit from inhaled nitric oxide in adults with ARDS.[3,4] A similar point can be made in the case of surfactant therapy, again shown to benefit premature neonates but not shown to benefit adults with ARDS.[5]

Does that mean that HFV has no role in the treatment of adult ARDS patients? From the available evidence, the best that can be said is that we do not know. There is presently insufficient evidence to support the use of HFV for the treatment of ARDS. As I attend respiratory care and critical care meetings throughout the country, I have heard

numerous anecdotes of how HFV "rescued" a dying patient with ARDS and "saved" him from a certain death. However, we only needto look at the nitric oxide story to be skeptical of such testimonials. In fact, I was one of the proponents of the use of inhaled nitricoxide for ARDS—but the results of properly conducted controlled studies showed that I was wrong!

To date, there is only one ventilator strategy that has been shown to reduce mortality in patents with ARDS. That is the use of a low tidal volume strategy. This has been conclusively demonstrated in the ARDS network study,[6] using good old-fashioned volume-controlled ventilation on a conventional ventilator. Perhaps the correct strategy lies not in the development of newer more complicated ventilators (which could be harmful in the hands of those without special training in their use), but rather in the correct use of available technology.

Dean Hess R PhD RRT FAARC
Harvard Medical School
Department of Respiratory Care
Massachusetts General Hospital
Boston, Massachusetts

REFERENCES

1. Hess DR, Gillette MA. Tracheal gas insufflation and related techniques to introduce gas flow into the trachea. Respir Care 2001; 46(2):119–129.
2. Gillette MA, Hess DR. Ventilator-induced lung injury and the evolution of lung-protective strategies in acute respiratory distress syndrome. Respir Care 2001;46(2):130–148.
3. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26(1):15–23.
4. Lundin S, Mang H, Smithies M, Stenqvist O, Frostell C. Inhalation of nitric oxide in acute lung injury: results of a European multicenter study. The European Study Group of Inhaled Nitric Oxide. Intensive Care Med 1999;25(9):911–919.
5. Anzueto A, Baughman RP, Guntupalli KK,Weg JG, Wiedemann HP, Raventos AA, Lemaire F, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group. N Engl J Med 1996;334(22): 1417–1421.
6. Ventilation with lower tidal volumes compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301–1308.

Reviews of Books and Other Media. Note to publishers: Send review copies of books, films, tapes, and software to RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104

Books, Films, Tapes, & Software

Chronic Lung Disease in Early Infancy. Richard D Bland and Jacqueline J Coalson, Editors. (Lung Biology in Health and Disease, Volume 137, Claude Lenfant, Executive Editor.) New York: Marcel Dekker. 2000. Hard-cover, illustrated, 1,062 pages, $235.

Despite a huge effort over the 35 years since its initial description to find the causes of and means for preventing chronic lung disease in premature infants, it remains a condition that occurs with substantial frequency. The most severe variants of chronic lung disease, which sometimes led to infants being ventilated for more than a year, seem to have almost disappeared. The separate wards found in some neonatal intensive care units for long-term ventilation have been closed. Despite this apparent reduction in severity, the overall birthweight-specific incidence has changed little, and few proven therapies clearly prevent chronic lung disease. With the improved survival of more and more immature infants, chronic lung disease continues to be an important problem in neonatal intensive care unit survivors. This book is an attempt to draw together the majority of people involved in researching the etiology, pathophysiology, and treatment of neonatal chronic lung disease over the past 35 years, with a major emphasis on lung biology.

The 4 stated goals of the editors in planning the book were (1) to present the important clinical and pathologic features of the disease, (2) to review lung development, injury, and repair, (3) to define what remains to be learned about neonatal lung injury, and (4) to relate the required needed information to potential therapeutic and preventive strategies. In fulfilling these goals the editors have succeeded admirably.

The book is divided into 5 sections, the first dealing with clinical aspects; chapters on the history, epidemiology, clinical aspects, lung function testing, radiography, pathology, respiratory care practices in ventilation, and nutrition issues are included. Part 2 is a review of normal and abnormal alveolar and airway development, including hormonal effects and the effects of reactive oxygen species. Part 3 concerns the normal and abnormal development of the pulmonary circulation and interstitial space of the lung. Part 4 deals with mechanisms of lung injury and repair during development. Part 5 deals with models of developmental lung injury and repair.

This layout does lead to some excessive repetition and overlap. For example, there is a chapter on the mechanisms of reactive species injury to alveolar epithelium, another on the molecular mechanisms of oxygen-induced lung injury, another chapter describes the assessment of tissue injury from reactive oxygen metabolites, and another chapter reviews oxygen and oxidants and their role in chronic lung disease. This led to 3 appearances of a list of reactive oxygen species and to 2 almost identical figures (appearing 16 pages apart) showing peroxidation of fatty acids. Although this sort of extensive multi-author text is liable to have such overlap and repetition, apart from this one example of oxygen toxicity/antioxidants and induced lung injury, the repetition has been kept to a minimum.

Particularly important, I think, is the chapter by Jacqueline Coalson, one of the co-editors of the volume, on the pathology of chronic lung disease of early infancy. The chapter compares "classic" bronchopulmonary dysplasia (BPD) pathology with BPD pathology in the current era ("new BPD"), and it is a clear and important review of the issue. I believe the distinct pathology of "new BPD" has been under-appreciated by neonatal clinicians, and this chapter at least should be required reading for clinicians. Indeed, the distinct pathology of "new BPD" calls into question whether all of the previous BPD research, particularly on the clinical aspects, remains completely relevant to today's surviving extremely immature infants.

For the most part, the chapters in the clinical section are clearly written and have appropriate and circumspect conclusions. The clinical chapters could all be characterized as narrative rather than systematic reviews. In other words, the choice of references and their interpretation are the result of the interests and knowledge of the reviewers. Such selectivity can have major effects on the conclusions reached. One minor example concerns the statement that inhaled furosemide has not been shown to be effective—a statement supported by a single reference. This is contradicted by the latest systematic Cochrane Collaboration review, including all 8 completed trials, which shows that a single dose of furosemide, given by inhalation, leads to significant changes in lung mechanics, if not in any clinical outcomes.[1] The discrepancies between the conclusions of systematic and narrative reviews are frequently large, and it has been demonstrated that narrative reviews such as these may, therefore, be misleading.[2,3] This should not be taken as a major criticism of this volume in particular, as such reviews are those most commonly found in textbooks, but surely the time has come for our review articles and book chapters to become more systematic, more inclusive, and, thus, more reliable.

In general the quality of the figures is good and there are very few mistakes or typographical errors. However, one of the figures (on page 548) is so badly reproduced that it is difficult to interpret, and in the chapter on interventions for tissue free radical injury the figures are all mislabeled.

I was unable at any point in the book to find even a brief analysis of the relationship between BPD and poor neurological function in the long term. This is a well recognized complication of BPD, probably as important to parents and patients as any of the issues dealt with in this book. And although it is clearly not the primary focus of this book, some analysis of the potential reasons for central nervous system dysfunction in surviving infants suffering chronic lung disease would, I think, have been useful. Even a single paragraph in the chapter on long-term outcome would have focused attention on this important issue. Also relevant to this issue, the section on corticosteroids in the drug treatment chapter only mentions reported transient cessations of somatic and brain growth, despite the fact that many studies are now reporting major disruption of central nervous system development in infants who receive postnatal steroids for BPD.

This book is, I believe, an extremely valuable source of information for anyone who has an interest in the biology of lung injury in the developing lung. Indeed, it is hard to

imagine any aspect of this field that has not received substantial attention in this volume. Each chapter is completed by a section in which the authors speculate about future important advances, and it will be interesting to see how many of these speculations are realized over the next few years. For a clinician, I think that the heavy emphasis on lung biology will provide extra insights and a greater understanding of pathophysiology.

Overall, I believe this book should be available in the library of any hospital that has a neonatal intensive care unit, and it is an important resource for those interested in the pathophysiology of lung injury in premature infants.

Keith J Barrington MB ChB
Department of Paediatrics
Royal Victoria Hospital
McGill University
Montreal, Quebec
Canada

REFERENCES

1. Brion LP, Primhak RA, Yong W. Aerosolized diuretics for preterm infants with (or developing) chronic lung disease (Cochrane Review). In: The Cochrane Library, 2, 2001. Oxford: Update Software.
2. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 1992;268(2):240–248.
3. Guyatt GH, Sinclair J, Cook DJ, Glasziou P. Users' guides to the medical literature: XVI. How to use a treatment recommendation. Evidence-Based Medicine Working Group and the Cochrane Applicability Methods Working Group. JAMA 1999; 281(19):1836–1843.

Voices and Choices: Young People Who Use Assisted Ventilation: Their Health and Social Care, and Education. Jane Noyes. Norwich, United Kingdom: The Stationery Office, 1999. Soft-cover, illustrated, 105 pages, £12.50, $20.50.

Voices and Choices: Young People Who Use Assisted Ventilation: Bibliography and Analysis of the Literature. John Sudbery and Jane Noyes. Norwich, United Kingdom: The Stationery Office, 1999. Soft-cover, illustrated, 94 pages.

The number of young people who use assisted ventilation because of illness or trauma has steadily increased over the last 20 years. Noyes's work documents and reinforces the observation, also made by others[1] that young people with disabilities may often be treated with concern and care, but not as "citizens with rights." Noyes explains that good practice, in addition to excellent treatment, also requires respect of the patient's rights, including a right to adequate services; a right to protection from abuse, neglect, and discrimination; and a right to information and to participate fully in decisions regarding his or her own life.

A theme throughout the reading is that patient participation is denied principally because of a medical attitude that is prescriptive and paternalistic. Prior studies had never presented young people's own feelings and opinions. Here their voices speak loud and clear. Noyes's protocol uses direct, in-depth interviews of young people age 6 to 18 years. When asked what sort of caregiver he likes, a young boy, age 15, answers: "Nice, not unhappy, not grumpy, and happy to look after me." A girl, also age 15, complains about not being informed: "I need to know everything that is happening, and what is going on."

It is also argued that the children's need for attachment and the right to adult protection should be recognized as parallel to their right to participation, which increases with age and understanding. Furthermore, a symbiotic relationship may exist between children and parents. The important role of the parents becomes especially evident when their children's wishes need to be interpreted. Parents can assist them in making decisions. Thus, Noyes also interviews parents. They feel that when the system supports decision-making by medical professionals and administrators without parents' participation, this negates the parents' responsibility and "claims parental ownership."

Noyes also includes examples of good practice in each chapter. When a boy, age 9, is considered as a possible candidate for a phrenic pacemaker implant, he does not like it. It makes him feel like a "robot." When his mother proposes that this decision is better postponed until he becomes older and can make his own mature judgment, all agree. In this case, the patient and family are included in the decision-making process.

To satisfy our professional interest we would like to know more when clinical, therapeutic procedures are mentioned. In the above case, did the options presented include state-of-the-art phrenic pacemaker implantation, and was this course of treatment compared with other ways of providing ventilation? We have to presume it was. Also, when the use of oxygen cylinders for Lisa, another young ventilator-dependent person, is criticized as wasteful compared to oxygen concentrators, we would like to know why. Was the use continuous? Did she have components of intrinsic pulmonary pathology? If not, the treatment of pure hypoventilation is assisted ventilation. Oxygen $> 21\%$, by itself, favors micro- to macro-absorption atelectasis, particularly in patients who hypoventilate. A cylinder may be kept for emergencies only. When continuous oxygen supplement is indicated but the patient can be active in and out of the house, liquid oxygen portable systems or lightweight oxygen containers may then be a better choice. When difficulties in tracheostomized patients are mentioned, there is no discussion of ways to obviate or alleviate these difficulties, such as noninvasive ventilation, ventilation with a deflated cuff and larger volumes, speaking tracheostomies, glossopharyngeal breathing, and the use of more recent biomedical engineering devices such as voice synthesizers.

This work, however, is not intended to be a vade mecum of respiratory therapy. It is instead a psychosocial study of personal approaches and systems of care regarding the relationship between the young ventilator-dependent patient and his or her own immediate social and physical environment. These interviews raise questions concerning prolonged stay in critical, acute, and adult hospital environments. There, young people may be exposed to long-lasting emotional trauma. Other problems are often poor discharge planning and fragmentation of care. This underscores the importance of early coordination and clarification of goals and roles. In fact, experience dictates that early discharge planning, assessment of resources, equipment, space, housing, and other needs should start immediately on admission to the hospital, and then be completed as information is gathered from the members of the team. Also, an adequate number of meetings with the family should take place for the exchange of information and for training. Discharge home is preferred unless the care would be inadequate because of exceptional circumstances. It is necessary to train the patient and family to familiarize them with the routines of care and to relieve the inherent anxiety before

discharge home. Often, a ventilator-dependent person may have mobility impairment and require a wheelchair or other equipment. Solving problems of accessibility and space at home may require time, so information should be gathered as soon as feasible after hospital admission, and a person needs to be identified to be responsible for a smooth continuum of coordinated care among vendors, home-care services, and authorizing state agencies.

Noyes relates that even after discharge, patients' families complain of having to deal with various and often apparently competing agencies responsible for medical services, social services, and education services. A unified strategy among providers of funds and services appears to be needed. This again brings out the necessity of a team coordinator, a case manager, who should be experienced in the field and have effective interpersonal skills to deliver a holistic, cost-effective, team approach. Another important family complaint is that often professionals and assigned caregivers, both in the hospital and after discharge home, may be less cognizant of the routines of care than the patient and the family. They lack familiarity with specific protocols and guidelines for the health and safety of these patients. Also, clarification of roles and the negotiation of boundaries regarding privacy, parenting, and caring may become even more critical once a patient is discharged. Caregivers should respect the privacy and the cultural identity of the family. Many other points are brought to attention that can be particularly important to providers of care and families.

Noyes organizes her material well, in 8 chapters: "Introduction," "Young People in Hospital," "Getting Home from Hospital," "Living at Home," "Starting or Returning to School," "Growing Up," "Young People Who Do Not Live with Their Families," and "Conclusions." She inquires about the treatment and feelings of these young patients from the day of hospital admission to the transition to adulthood. The chapters are divided into subsections, which are helpful for easy consultation. In the section on "Growing Up," a couple of the subtitles are "Social Inclusion" and "Sexuality." Sexuality, as well as other intimate, sensitive subjects, is not discussed in-depth during the interviews, but the young people's interest and the importance of the subject is evident.

Comments and bibliography are found in the companion publication, **Young People Who Use Assisted Ventilation. Bibliography and Analysis of the Literature**, in which it is stated that the subject may also raise sensitive issues for caregivers and would benefit from further consideration in the literature. This companion publication, reviewing the literature from a more analytical and academic point of view, also regards the psychosocial picture from the perspective of the young people and their families (the consumer), but also includes other sections related to the subject: "The Services," "The Law," and "Finance." Here the authors admit that they excluded the purely clinical literature and, also for technical reasons, their search strategy "produced only few references on the topic of communication and the related rehabilitation issues." But otherwise, their review of the bibliography is: "extensive, if not exhaustive."

Some of the arguments treated in the analysis are "Friendships and Relationship Needs," "Employment," "Child Abuse, Child Protection, and the Criminal Justice System," "Parents as Caregivers," and "Individual and Family Finance." Both publications include, at the end, very useful sections regarding "Conclusions and Key Messages" and lists of future goals and research the authors deem necessary. For example, this agenda includes compilation of "a register of the number and status of the young people involved and guidelines for audit by regional and national health authorities" and also "more study and attention should be given to ways that could enhance the participation of these young people in social life."

Noyes's project was started in 1997, and published in 1999. It was supported as part of a program of research and innovative projects for the consideration of practitioners and policy makers. The study was conducted in the context of the United Kingdom's nationalized health system, but concepts of quality of care should be universal.

Noyes's **Voices and Choices: Young People Who Use Assisted Ventilation** is the diligent labor of a patient's advocate. The presentation is intended to be accessible to ventilator-dependent young people and their families and advocates, who should know their rights as well as their responsibilities and the importance of coordination with members of the professional team. The book may be perceived as pedantic and simplistic, but it gives important information and a basis for the appreciation of psychosocial considerations, knowledge of the existence of established consensus guidelines, and ongoing questions on the subject. These 2 companion publications leave us with the impression of a system that, ideally, wants to guarantee basic rights and excellent care but often gets entangled in a heavy bureaucratic load and managerial inefficiency, possibly due to unrealistic assessments of funding levels. But there is also evidence that efforts are being made to study and improve the system. In the **Bibliography and Analysis of the Literature** the authors report that since 1997, when Noyes started her project, there have been other publications on these subjects and some governmental action has occurred in the United Kingdom. They recognize that the American literature, including governmental literature, has dealt with the problem of ventilator-dependency for a longer time. A comparative analysis, including outcomes, based on longitudinal studies of this problem would be of interest. Given the scarcity of psychosocial consideration in the overwhelmingly analytical and coolly dispassionate clinical material, Noyes's work would be good reading for all students and professionals in respiratory therapy, pediatric care, nursing, and all other interested professionals. For social workers, patients' advocates, administrators, legislators, and students more involved in psychosocial aspects of the subject, the **Bibliography and Analysis of the Literature** should be of great interest, and the tandem publications would be useful additions to their libraries.

Redento D Ferranti MD
Gaylord Hospital
Department of Medicine
Yale University School of Medicine
New Haven, Connecticut

John J Votto DO
Hospital for Special Care
New Britain, Connecticut
Department of Clinical Medicine
University of Connecticut
School of Medicine
Farmington, Connecticut

REFERENCE

1. Baldwin S, Carlisle J. Social support for disabled children and their families: a review of literature. Edinburgh: HMSO, 1994.

Cystic Fibrosis: Medical Care. David M Orenstein MD, Beryl J Rosenstein MD, Robert C Stern MD, Editors. Philadelphia: Lippincott, Williams & Wilkins. 2000. Softcover. 365 pages, $39.95.

Clinical and scientific developments in the diagnosis and treatment of cystic fibrosis (CF) have altered the course of this disease. Molecular characterization of the gene defects has increased our insight into the nature and variety of CF. The availability of antibiotics, nutritional support, ventilators, and endoscopic procedures dramatically increased the life expectancy of CF patients. The time when death in the teen years was the common outcome for CF patients is so recent that, as the authors observe, adult pulmonary medicine has only just started concentrating on the management of CF. The extension of the life span of these patients has created a labyrinth of manifestations, complications, and possible courses that would make CF unrecognizable to those who first described "cystic fibrosis of the pancreas," 60 years ago, as an invariably lethal disease of infants.

CF medical care today is dominated by the multisystemic character of this disease, the increasing perplexity of its clinical course, and the need for effective communication among care providers coming from different specialties and professions. Given rapid technologic advances and increasing awareness, updated presentations of the practical aspects of CF medical care will continue to be a necessity. This book aims at fulfilling these needs. The readership is wide and includes physicians, nurses, epidemiologists, geneticists, and therapists. The material is selected by 3 internationally acclaimed experts in CF treatment, with combined experience of more than 80 years.

The book is organized into 12 chapters, progressing in a logical way from the molecular and cellular background and major organ systems affected by CF, to medical management, surgery, hospitalization, and terminal care. References follow each chapter and are limited to a reasonable number, providing adequate information for further reading. The language is clear. The authors successfully present facts as well as arguments and differences of opinion without losing their focus—a comprehensive approach to CF care. The tables are very informative and the figures are illustrative and carefully selected.

The chapter on the diagnosis of CF features phenotype/genotype associations, calculated recurrence risk tables for relatives of CF patients, and presenting symptoms of CF patients. The description of the sweat test, its method, limitations, and specificity, is concise and to the point. The tables with indications for sweat testing and conditions associated with elevated sweat electrolyte concentration are comprehensive and helpful. Caveats are included, as well as screening algorithms.

The chapter on the respiratory system is extensive and covers the subjects of pulmonary exacerbation, immunization, choice of antibiotics, chronic inflammation, upper airway problems, bronchopulmonary aspergillosis, and complications. Many controversies have arisen around these issues. Opposing views are presented impartially while the need for common sense and consideration of the individual patient's problems is dealt with in a thoughtful manner. Interesting topics include chest pain, hemoptysis, and wheezing in infancy. The effect of high-dose ibuprofen in slowing the progression of pulmonary lesions is also discussed.

The chapter on the gastrointestinal system is superbly written, with very informative paragraphs on the distal intestinal obstruction syndrome (formerly referred to as meconium ileus equivalent), gastroesophageal reflux, and CF liver disease. Pancreatic enzyme replacement is discussed extensively, with special emphasis on the issues of abdominal pain, constipation, and bloody diarrhea. There is ample information on electrolyte imbalance, vitamin deficiency, and caloric deficit. This chapter features a discussion of fibrosing colonopathy, a newly-recognized and unusual complication associated with administration of high doses of pancreatic enzymes, resulting in irreversible damage of the large bowel. The differential diagnosis of abdominal pain in CF is discussed briefly, but the omission of a table with causes of abdominal pain in CF makes itself felt. Involvement of other organs is presented in the following chapter, which is divided into cardiovascular, endocrine, reproductive, renal, and other aspects of CF.

The inclusion of a chapter on exercise is justified. The authors address several misconceptions associated with exercise in CF. The dual importance of physical fitness as both a marker of life quality and possibly as a factor contributing to well being is discussed. Model exercise programs are presented. Hospitalization is discussed in a separate chapter, with extremely helpful tips on psychosocial, insurance, and research issues. The tables on "how to be a well adjusted and successful hospital patient" and "pitfalls in patient and family communication" could prevent many a foreseeable misunderstanding. Medical subjects in the same chapter include preventive measures against transmission of *Burkholderia cepacia*, differential diagnosis of fever, and a number of practical tips on venous access, collection of arterial blood samples, and use of local anesthesia.

Surgical aspects of CF are presented in an easy-to-follow, comprehensive chapter. An excellent discussion of the management of pneumothorax is included. Other interesting topics are surgical management of gastroesophageal reflux, enteral feeds, meconium ileus, and intussusception. The anesthetic caveats in the same chapter are very intriguing and conveniently illustrated with 2 tables. Transplantation issues in CF are dealt with extensively. Timing of referral for lung transplantation, care while awaiting transplant, specific problems associated with pneumothorax in CF, the technique of living lobar transplant, and post-transplant care are among the most attractive topics of this book. The discussion of liver transplant in CF is also very thorough.

A chapter on adolescents and adults is included, but appears to be rather short considering the massive expansion of this part of the CF population in the last 30 years. The chapter on terminal care is very informative, with the appropriate emphasis on psychosocial and family aspects. Predicting the time of death; treatment of dyspnea, hypoxemia, and hypercapnia; the use of oxygen, β adrenergic agonists, theophylline, and morphine in the terminally ill patient are discussed. A table with signs of altered blood gases is featured.

Three appendixes are included. Appendix A features a detailed plan for long-term management, backed with references. Useful recommendations on laboratory testing, pulmonary function monitoring, and imaging are presented in Appendix B. Appendix C is a directory of CF care centers. This appendix is appropriately placed at the end of the book to stress for one last time the point repeated persistently by the authors: continuity of care is of paramount importance and optimal care is provided in CF centers. The index makes it easy to use this book as its authors intended: as a quick ref-

erence. Its convenient size and price contribute to its appeal.

In conclusion, the authors achieved their goal of creating a helpful tool for the management of a complex, frustrating, and changing disease. They produced an appealing, balanced, easy-to-read text that is a valuable reference for the specialist and also an excellent introduction to the practices of CF care for the neophyte. This practical and concise book will be welcomed by all health care professionals caring for CF patients.

Demetrios S Theodoropoulos MD
Division of Allergy/
Immunology/Rheumatology
Rainbow Babies and Children's Hospital
Case Western Reserve University
School of Medicine
Cleveland, Ohio

Pulmonary Rehabilitation: Guidelines to Success. 3rd Edition. John E Hodgkin MD, Bartolome R Celli MD, Gerilynn L Connors RRT. Philadelphia: Lippincott, Williams & Wilkins, 2000. Hard-cover, 726 pages, $62.

Pulmonary rehabilitation has remained an area in which respiratory therapists can make substantial contributions to the lives of people suffering chronic obstructive pulmonary disease (COPD) and other cardiopulmonary disorders. The demographics of the population of the United States indicate that along with the aging population comes an increased number of individuals with chronic illness. Pulmonary rehabilitation will play an important role in the lives of an increasing number of people. In addition, the cost-effectiveness of pulmonary rehabilitation dictates its widespread inclusion in respiratory care practice. This book brings together a multidisciplinary team of experts, domestic and international, to present a comprehensive up-to-date treatment of pulmonary rehabilitation. Reference sections at the end of each chapter attest to the currency of content and allow the reader to seek out additional information if desired. The preface of the first edition states that the book is directed to both physicians and related health disciplines. Given the team nature of pulmonary rehabilitation and the use of multidisciplinary contributing authors, directing the book to multiple groups is appropriate.

The current edition begins with the history of pulmonary rehabilitation, its development, and the basic constructs that define pulmonary rehabilitation. Following the introductory sections are 5 additional sections that address therapeutic intervention, special situations and concerns, application in non-COPD patient populations, international perspective, and the future of pulmonary rehabilitation.

The book is very well organized, with each chapter beginning with objectives and ending with a comprehensive reference list. Charts, tables, figures, and illustrations are employed efficiently and enhance rather than detract from the written text. Sections and the chapters within each section are organized in a logical fashion, with each building on the information from earlier chapters. The book presents up-to-date, well-referenced data, adding to the credibility of the text. An appreciated feature of the book is adherence to style throughout—a feature sometimes lacking in works with many contributing authors. Also refreshing is the lack of meaningless distracters such as chapter questions and excessive reliance on flashy "state of the art" attempts at pedagogical trends. While some educators find these features helpful in course organization tasks, I find that the traditional text approach allows the instructor and the audience more freedom in directing discussions related to section or chapter content.

The first section of the book covers pulmonary rehabilitation from a historical perspective. The single chapter in this section successfully presents background regarding the development of components of pulmonary rehabilitation, such as patient and family education, smoking cessation, psychosocial concerns, physical procedures, and medical treatment, including medications and delivery techniques. Of particular interest was the discussion of the advent of intermittent positive-pressure breathing and its misuse. The author does not debate the use of intermittent positive-pressure breathing in COPD, but presents an argument based on several studies. The author ends the chapter with helpful experience-based commentary that includes useful considerations often overlooked when dealing with COPD patients, such as the effects of maldistribution of ventilation on arterial blood gas equilibration time. The chapter is very well referenced, demonstrating the depth of historical and current literature cited.

In Section II, "Basic Concepts of Pulmonary Rehabilitation," the reader is treated to 5 chapters dedicated to establishing a common basis for understanding later sections and chapters. Information covered includes the definition and characteristics of pulmonary rehabilitation, patient selection and assessment of COPD, pathophysiology of COPD, assessment of dyspnea, and patient and family education. Chapter 3 within Section II presents models for patient selection and exclusion that are clear, concise, and applicable. Chapter 4 presents a concise review of pathophysiology, which includes clear, easily interpretable charts and diagrams. One figure (Fig. 4.9), is exceptionally useful, as it depicts an integration of the many components that influence breathing in the COPD patient and suggests the various strategies to treat the disorder. Chapter 6 discusses patient and family education and addresses how to teach. The chapter includes concise sections on various learning theories and potential client characteristics and their possible learning needs. It does not spend much time on the educational content for pulmonary rehabilitation, but instead wisely uses the space to help the reader realize that teaching is a skill based on research and that patient outcome may be enhanced by helping the client learn the content well.

Section III gets into the nuts and bolts of pulmonary rehabilitation and includes 12 chapters on the therapeutic interventions appropriate for pulmonary rehabilitation. These chapters encompass a wide range of subjects, such as pharmacology, ventilatory muscle training, tobacco dependence, and sexuality in the pulmonary patient. The section ends with a well-written chapter covering the preventive aspects for the patient with chronic lung disease. Each chapter in this section is comprehensive and employs diagrams and tables sparingly but effectively. Chapter 15 presents information about tobacco dependence and presents a useful case study. Other chapters could have been enhanced with the inclusion of case studies. Case studies help the reader see the information applied and help bridge the gap between theory and practice.

Section IV presents a variety of special considerations in pulmonary rehabilitation, such as ethical issues, surgical therapy, travel, sleep disorders, marketing and reimbursement issues, and chapters on home mechanical ventilation in the United States and Europe. Chapter 20 does a nice job of presenting various pulmonary rehabilitation outcome assessment strategies and includes recent research results for such variables as baseline dyspnea index, transitional dyspnea index, chronic respiratory disease question-

naire, and physiologic adaptation to exercise. The chapter is very comprehensive and provides many possible outcome assessment approaches. Chapters 21 and 22 provide a complete review of home mechanical ventilation, including objectives for home caregivers. Chapter 22, although brief, gives the reader an overview of home mechanical ventilation in Europe and provides a basis for important comparisons regarding reimbursement differences. If the United States adopts a universal or national health insurance plan, the "heads-up" information in this chapter will prove beneficial. Chapter 23 clearly outlines surgical treatment possibilities for advanced pulmonary disease patients, including indications, procedural descriptions, and anticipated outcomes. The additional chapters in Section IV are equally comprehensive and collectively provide a well-rounded body of information regarding special considerations in pulmonary rehabilitation.

Section V presents 3 chapters addressing pulmonary rehabilitation as applied to pediatric, non-COPD, and neuromuscular patient populations.

Chapter 31 covers ventilation techniques and physical medicine interventions for neuromuscular patients. A historical perspective is woven into the chapter, making the information presented quite comprehensive. Manually assisted coughing, mechanical insufflation-exsufflation, and other airway clearance techniques are included.

Chapter 32 describes rehabilitation in the non-COPD population and includes indications and research results, providing a clear rationale for this group's inclusion in pulmonary rehabilitation programs.

Finally, Chapter 33 presents pediatric disorders and the application of pulmonary rehabilitation procedures to diseases afflicting these groups. The chapter depth is such that the reader would have had to read previous chapters in order to apply the concepts related to the pediatric patient.

Section VI presents 6 chapters regarding the international perspective on pulmonary rehabilitation. These chapters collectively not only provide the reader with a basis for comparisons among the countries represented, but also impress the reader that medicine is practiced in a global community. Other texts within our discipline would be wise to follow this example as countries become less isolated and the practice of medicine becomes more sophisticated. The international comparisons in this section are, again, quite comprehensive. Each country is presented in a separate chapter and it requires the reader to shuttle back and forth to make comparisons. A summary chart of all countries presented would be a useful visual.

Section VII comprises a single chapter, which summarizes the benefits of pulmonary rehabilitation. Each component of a pulmonary rehabilitation program is addressed. The chapter additionally addresses the current and future concerns facing pulmonary rehabilitation programs, such as reimbursement issues and patient screening. The chapter ends with suggested research possibilities for pulmonary rehabilitation.

The overall strengths of this book include its comprehensiveness and its concise, to-the-point text. Additionally, adherence to style makes the book easy to comprehend. The sparing use of tables and diagrams is refreshing in that the reader is not distracted by flashy splashes of color, drawing attention away from the content. Section summary charts or diagrams would help compare the large amount of information held in the chapters. Perhaps more case studies would help bring information to the applied level. The book is well written in traditional fashion, with up-to-date information and research reports. The reading level appears appropriate for physicians, in-service educators, and various health practitioners. Health care students in baccalaureate programs would adapt well to this text, but it may prove challenging to recent high school graduates. I would highly recommend this book to a variety of educational programs.

Ronald G Beckett PhD RRT
Respiratory Care Program
Department of Cardiopulmonary Sciences
and Diagnostic Imaging
Quinnipiac University
Hamden, Connecticut

Advances in Cardiopulmonary Rehabilitation. Jean Jobin PhD, François Maltais MD, Pierre LeBlanc MD, Clermont Simard PhD, Editors. Champaign, Illinois: Human Kinetics, 2000. Hard-cover, illustrated, 323 pages, $42.

Controlled, randomized studies and meta-analyses have clearly established that pulmonary rehabilitation, once recognized as "an art of medical practice," reduces symptoms, increases functional ability, and improves health-related quality of life in individuals with chronic respiratory diseases, even in the face of irreversible abnormalities of lung architecture. Therefore, in the new millennium it is no longer a question of *if*, but of who, how, when, and where does pulmonary rehabilitation work. This book tries to answer most of those questions.

This well constructed and well referenced volume reports a series of articles reviewing some topics of the First Quebec International Symposium on Cardiopulmonary Rehabilitation held in 1999. This is an impressive example of "overseas efficiency," given the short delay between the symposium and publication of the related book with "fresh" material.

The book's 8 parts comprise 22 chapters reflecting the reality of cardiopulmonary rehabilitation at the end of the second millennium. After the first part summarizes the history and actual status of rehabilitation, the following sections present the general sequence in which patients are integrated into cardiopulmonary rehabilitation programs. Optimizing medical treatment is the first step, followed by current and upcoming issues related to selection and recruitment of candidates. The central parts describe the most recent advances in cardiac and pulmonary rehabilitation, exercise as the cornerstone of any rehabilitation intervention, and some aspects of rehabilitation, including economic impact. The last parts cover issues of quality of life, which is considered a key outcome in rehabilitation, and future perspectives.

Although the majority of chapters are review articles, some authors have reported their original studies, and each chapter is challenging through its discussion of important controversies. The intended audience is physicians, cardiorespiratory physiologists and therapists caring for patients with heart or lung problems, and those involved in cardiac and pulmonary rehabilitation. There is no specific profession-dedicated chapter, so both physicians and therapists may enjoy all chapters. Despite the few illustrations, the reader is well introduced to the topics, the style of most of the authors is clear, and the editors strive to stimulate the reader to promote pulmonary rehabilitation programs in the face of the reported unsatisfactory recruitment of patients by pulmonary rehabilitation programs in North America.

According to the European Respiratory Society, the aims of pulmonary rehabilitation should be "to restore patients to an independent, productive, and satisfying life

and prevent further clinical deterioration to the maximum extent compatible with the stage of the disease"—a definition somehow attributing to pulmonary rehabilitation an effect on the natural history of the disease.[1] More recently, the European Respiratory Society Task Force Position Paper defined pulmonary rehabilitation as "a process that systematically uses scientifically based diagnostic management and evaluation options to achieve the optimal daily functioning and health-related quality of life of individual patients suffering from impairment and disability due to chronic respiratory disease, as measured by clinically and/or physiologically relevant outcome measures."[2] This definition does not seem to be very different from that developed by the National Institutes of Health Workshop on Pulmonary Rehabilitation Research: "Pulmonary rehabilitation is a multidimensional continuum of services directed to persons with pulmonary disease and their families, usually by an interdisciplinary team of specialists, with the goal of achieving and maintaining the individual's maximum level of independence and functioning in the community."[3]

Nevertheless, when examining the pulmonary rehabilitation components, some differences appear, mainly related to the comprehensive treatment of respiratory diseases. On the other side, the European perspective includes a wider spectrum of pulmonary rehabilitation programs than in North America. There are some topics considered in the European perspective that are not considered in the American one, such as respiratory muscle rest (ie, long-term home mechanical ventilation), long-term oxygen therapy, nutritional therapy, and nursing care. This leads to a European pulmonary rehabilitation concept near to chronic care. Furthermore, in Europe, institutions primarily devoted to pulmonary rehabilitation have developed intermediate intensive care units aimed at treatment of acute-on-chronic respiratory failure (mainly by noninvasive mechanical ventilation) and at long-term difficult weaning from mechanical ventilation.

This new volume seems to be evidence of the different concepts of pulmonary rehabilitation on the 2 sides of the Atlantic. Although the term *cardiopulmonary rehabilitation* included in the title sounds rather disappointing to European ears, the content of the volume is better than the title. Indeed, despite the title, the authors of the chapters have dealt with cardio or pulmonary rehabilitation, which is nearer to the European concept of pulmonary rehabilitation. For example, the summary of the chapter on historical review of cardiopulmonary rehabilitation is based on the plan of action of the American Heart Association, and among the well-quoted 53 references of that chapter, only 2 titles include the term "pulmonary." This is not a criticism; it is an appreciation that the editors and chapter authors have a definite awareness of the differences between these 2 fields of rehabilitation.

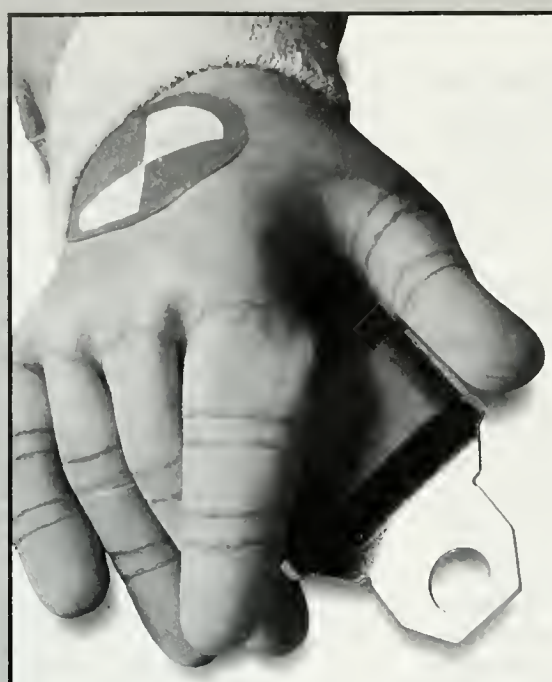
Despite this, there is a successful attempt to define the common field. That is, exercise training and peripheral muscle dysfunction in diseases such as chronic heart failure and chronic obstructive pulmonary disease. Now, there is no question about the fashionable need to have a more "holistic" clinical framework for our patients. To state this is different than to consider cardiac and pulmonary rehabilitation as a unique therapeutical tool. As clearly established in the chapter on "Horizons of Pulmonary Rehabilitation," "there are similarities but also distinct differences between the application of rehabilitation principles to patients with pulmonary versus cardiac diseases." A specific discipline is defined by the availability of (1) specific outcome measurements and (2) a "contra-science"; that is, a science with which to exchange information and progress. For example, for pulmonary rehabilitation the contra-science is clearly respiratory physiology (or pathophysiology). A cardiologist would not agree with this definition of contra-science for cardiac rehabilitation, would he? Furthermore, from the chapters devoted to the outcome measures, the reader gets the correct impression that the outcome measures cannot be indifferently used in either field without any specific validation.

In summary, I enjoyed this nice book and after reading it I feel to have added a little to my knowledge of pulmonary rehabilitation. It is not a negligible result.

Nicolino Ambrosino MD
Lung Function and Pulmonary Unit
Salvatore Maugeri Foundation
Istituti di Ricovero e Cura a
Carattere Scientifico
Scientific Institute of Gussago
Gussago, Italy

REFERENCES

1. Donner CF, Howard P. Pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD) with recommendations for its use. Report of the European Respiratory Society Rehabilitation and Chronic Care Scientific Group (SEPCR Rehabilitation Working Group). Eur Respir J 1992;5(2): 226–275.
2. Donner CF, Muir JF. Selection criteria and programmes for pulmonary rehabilitation in COPD patients. Rehabilitation and Chronic Care Scientific Group of the European Respiratory Society. Eur Respir J 1997;10(3):744–757.
3. Fishman AP. Pulmonary rehabilitation research. Am J Respir Crit Care Med 1994; 149(3 Pt 1):825–833.



U.S. Department of Transportation

"Vince & Larry ®" ©1985 U.S. DOT

AVOIDING A TICKET IS A SNAP

YOU COULD LEARN A LOT FROM A DUMMY.®

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page of

Form Approved: OMB No. 0910-0291 Expires: See OMB statement

FDA Use Only (Hosp Care)

Triage unit sequence #

A. Patient information

1 Patient identifier	2 Age at time of event or Date of birth:	3 Sex	4 Weight
In confidence		☐ female ☐ male	____ lbs or ____ kgs

B. Adverse event or product problem

1 ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2 Outcomes attributed to adverse event (check all that apply)

- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other.

3 Date of event (mo/day/yr)	4 Date of this report (mo/day/yr)

5 Describe event or problem

6. Relevant tests/laboratory data, including dates

7 Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1 Name (give labeled strength & mfr/labeler, if known)

#1

#2

2 Dose, frequency & route used	3 Therapy dates (if unknown, give duration) (from/to or best estimate)
#1	#1
#2	#2

4 Diagnosis for use (indication)	5 Event abated after use stopped or dose reduced
#1	#1 ☐ yes ☐ no ☐ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7 Exp. date (if known)	8 Event reappeared after reintroduction
#1	#1	#1 ☐ yes ☐ no ☐ doesn't apply
#2	#2	#2 ☐ yes ☐ no ☐ doesn't apply

9 NDC # (for product problems only)

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1 Brand name

2 Type of device

3 Manufacturer name & address	4 Operator of device
	☐ health professional ☐ lay user/patient ☐ other

6.
model #
catalog #
serial #
lot #
other #

5. Expiration date (mo/day/yr)

7. If implanted, give date (mo/day/yr)

8 If explanted, give date (mo/day/yr)

9 Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)

10 Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1 Name & address	phone #

2 Health professional?	3 Occupation	4 Also reported to
☐ yes ☐ no		☐ manufacturer ☐ user facility ☐ distributor

5 If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500 1/96)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number

Please do NOT return this form to either of these addresses.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA Form 3500-back

Please Use Address Provided Below – Just Fold In Thirds, Tape and Mail

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE, MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

American Association for Respiratory Care

MEMBERSHIP APPLICATION

Please read the eligibility requirements for each of the classifications in the right-hand column, then complete the applicable section. All information requested below must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

- ☐ Active
- Associate
  - ☐ Foreign
  - ☐ Physician
  - ☐ Industrial
- ☐ Special
- ☐ Student

Last Name _____

First Name _____

Social Security No. _____

Home Address _____

City _____

State _____ Zip __ __ __ __ __ — __ __ __ __

Phone No. (_____) _____

Primary Job Responsibility (check one only)

- ☐ Technical Director
- ☐ Assistant Technical Director
- ☐ Pulmonary Function Specialist
- ☐ Instructor/Educator
- ☐ Supervisor
- ☐ Staff Therapist
- ☐ Staff Technician
- ☐ Rehabilitation/Home Care
- ☐ Medical Director
- ☐ Sales
- ☐ Student
- ☐ Other, specify _____

Type of Business

- ☐ Hospital
- ☐ Skilled Nursing Facility
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Educational Institution
- ☐ Manufacturer or supplier
- ☐ Other, specify _____

Date of Birth (optional) _____ Sex (optional) _____

U.S. Citizen? _____ Yes _____ No

Have you ever been a member of the AARC? _____

If so, when? From _____ to _____

Preferred mailing address: ☐ Home ☐ Business

For office use only

FOR ACTIVE MEMBER

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care OR (3) holds a credential issued by the NBRC. An individual who is an AARC Active Member in good standing on December 8, 1994 will continue as such provided his/her membership remains in good standing.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Medical Director/Medical Sponsor _____

FOR ASSOCIATE OR SPECIAL MEMBER

Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available. Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

FOR STUDENT MEMBER

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

School/RC Program _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Length of program

- ☐ 1 year
- ☐ 2 years
- ☐ 4 years
- ☐ Other, specify _____

Expected Date of Graduation *(REQUIRED INFORMATION)*

Month _____ Year _____

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • (972) 243-2272 • Fax (972) 484-2720

Demographic Questions

We request that you answer these questions in order to help us design services and programs to meet your needs.

Check the Highest Degree Earned

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

Job Status

- ☐ Full Time
- ☐ Part Time

Credentials

- ☐ RRT
- ☐ CRT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

Salary

- ☐ Less than $10,000
- ☐ $10,001-$20,000
- ☐ $20,001-$30,000
- ☐ $30,001-$40,000
- ☐ $40,000 or more

PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation of $11.50 from my dues for each of these publications.

NOTE: Contributions or gifts to the AARC are not tax deductible as charitable contributions for income tax purposes. However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result of association lobbying activities. The AARC estimates that the nondeductible portion of your dues — the portion which is allocable to lobbying — is 26%.

Signature _____

Date _____

Membership Fees

Payment must accompany your application to the AARC. Fees are for 12 months. (NOTE: Renewal fees are $75.00 Active, Associate-Industrial or Associate-Physician, or Special status; $90.00 for Associate-Foreign status; and $45.00 for Student status).

☐ Active	$ 87.50
☐ Associate (Industrial or Physician)	$ 87.50
☐ Associate (Foreign)	$102.50
☐ Special	$ 87.50
☐ Student	$ 45.00
TOTAL	$_____

Specialty Sections

Established to recognize the specialty areas of respiratory care, these sections publish a bi-monthly newsletter that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

☐ Adult Acute Care Section	$15.00
☐ Education Section	$20.00
☐ Perinatal-Pediatric Section	$15.00
☐ Diagnostics Section	$15.00
☐ Continuing Care-Rehabilitation Section	$15.00
☐ Management Section	$20.00
☐ Transport Section	$15.00
☐ Home Care Section	$15.00
☐ Subacute Care Section	$15.00
TOTAL	$_____

GRAND TOTAL = Membership Fee plus optional sections $_____

☐ Total Amount Enclosed/Charged $_____

☐ Please charge my dues (see below)

To charge your dues, complete the following:

☐ MasterCard

☐ Visa

Card Number

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Card Expires _____/_____

Signature _____

Mail application and appropriate fees to:

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • [972] 243-2272 • Fax [972] 484-2720

Manuscript Preparation Guide

RESPIRATORY CARE welcomes original manuscripts related to the science and technology of respiratory care and prepared according to the following instructions and the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (available at *http://www.icmje.org/index.html*). Manuscripts are blinded and reviewed by professionals with experience in the subject of the paper. Authors are responsible for obtaining written permission from the original copyright holder to use previously published figures and tables. Before publication, authors receive page proofs and are allowed to make only minor corrections. Accepted manuscripts are copy-edited for clarity, concision, and consistency with RESPIRATORY CARE's format. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission. Editorial consultation is available at any stage of planning or writing: contact the Editorial Office, 600 Ninth Avenue, Suite 702, Seattle WA 98104, (206) 223-0558, fax (206) 223-0563, E-mail: rejournal@aarc.org

Categories of Articles

Research Article: A report of an original investigation (a study). Must include: Title Page, Abstract, Key Words, Introduction, Methods, Results, Discussion, Conclusions, and References. May also include: Tables, Figures (if so, must include Figure Legends), Acknowledgments, and Appendixes.

Review: A comprehensive, critical review of the literature and state-of-the-art summary of a topic that has been the subject of at least 40 published research articles. Must include: Title Page, Outline, Abstract, Key Words, Introduction, Review of the Literature, Summary, and References. May also include: Tables, Figures (if so, must include Figure Legends), Acknowledgments, and Appendixes.

Overview: A critical review of a pertinent topic that has fewer than 40 published research articles. Same structure as Review Article.

Update: A report of subsequent developments in a topic that has been critically reviewed in RESPIRATORY CARE or elsewhere. Same structure as a Review Article.

Special Article: A pertinent paper not fitting one of the other categories. Consult with the Editor before writing or submitting such a paper.

Editorial: A paper addressing an issue in the practice or administration of respiratory care. It may present an opposing opinion, clarify a position, or bring a problem into focus.

Letter: A brief, signed communication responding to an item published in RESPIRATORY CARE or about other pertinent topics. Tables, Figures, and References may be included. The letter should be marked "For Publication."

Case Report: Report of an uncommon clinical case or a new or improved method of management or treatment. A case-managing physician must either be an author or furnish a letter approving the manuscript. Must include: Title Page, Abstract, Key Words, Introduction, Case Summary, Discussion, and References. May also include: Tables, Figures (if so, must include Figure Legends), and Acknowledgments.

Point-of-View: A paper expressing personal but substantiated opinions on a pertinent topic. Must include: Title Page, Text, and References. May also include: Tables and Figures (if so, must include Figure Legends).

Drug Capsule: A miniature review paper about a drug or class of drugs. Drug Capsules address pharmacology, pharmacokinetics, and/or pharmacotherapy.

Graphics Corner: A brief, instructive case report discussing and illustrating waveforms for monitoring or diagnosis. Must include: Questions, Answers, and Discussion.

PFT Corner: A brief, instructive case report arising from pulmonary function testing, accompanied by a review of the relevant physiology and appropriate references to the literature. Must include: Questions, Answers, and Discussion.

Test Your Radiologic Skill: A brief, instructive case report pertinent to respiratory care and involving imaging, including one or more radiographs or other images submitted as black and white glossy photographs that clearly illustrate the teaching points being made. Must include: Questions, Answers, and Discussion.

Preparing the Manuscript

Double-space the text and number the pages. Do *not* include author names, author institutional affiliations, or allusions to institutional affiliations anywhere except on the title page. On the Abstract page include the title but do not include author names. Begin each of the following on a new page: Title Page, Abstract, Text, Acknowledgments, References, each Table, each Figure, and each Appendix. Use standard English in the first person and active voice. Type all headings in initial-capital letters (eg, Introduction, Methods, Patients, Equipment, Statistical Analysis, Results, Discussion). Center the main section headings and place second-level headings on the left margin.

Abstract. Please ensure that the abstract does not contain any facts or conclusions that do not also appear in the body text. Limit the abstract to no more than 250 words.

Key Words. Include a list of 6 to 10 key words or key phrases in Research Articles, Reviews, Overviews, Special Articles, and Case Reports. Key words are best selected from the Medical Subject Headings (MeSH) used by MEDLINE and available at *http://www.nlm.nih/gov/mesh/Mbrowser.html*.

References. Assign reference numbers in the order that articles are cited in your manuscript. At the end of the manuscript, list the cited works in numerical order. Abbreviate journal names as in *Index Medicus*. List all authors. If the research has not yet been accepted for publication, cite the research as a personal communication (eg, Smith KR, personal communication, 2001); *however, you must obtain written permission from the author to cite his or her unpublished data.* Do not number such references; instead, make parenthetical reference in the body text of your manuscript. Example: "Recently, Jones et al found this treatment effective in 45 of 83 patients (Jones HI, personal communication, 2000)."

The following examples show RESPIRATORY CARE's style for references.

Paper accepted but not yet published:

Hess D. New therapies for asthma. Respir Care (year, in press).

Article in a journal carrying pagination throughout the volume:

Legere BM, Kavuru MS. Pulmonary function in obesity. Respir Care 2000;45(8):967-968.

Article in a publication that numbers each issue beginning with Page 1:

Kallstrom TJ. Focus on asthma—disease management: a role for the respiratory therapist. AARC Times 1999;23(Oct):16, 17, 19.

Corporate author journal article:

American Association for Respiratory Care. Clinical Practice Guideline. Removal of the endotracheal tube. Respir Care 1999;44(1):85-90.

Article in journal supplement: (Journals differ in numbering and identifying supplements. Supply information sufficient to allow retrieval.)

Barnes PJ. Endogenous inhibitory mechanisms in asthma. Am J Respir Crit Care Med 2000; 161(3 Pt 2):S176-S181.

Abstract in journal: (Abstracts citations are to be avoided, and those more than 3 years old should not be cited.)

Volsko TA, De Fiore J, Chatburn RL. Acapella vs flutter: performance comparison (abstract). Respir Care 2000;45(8):991.

Editorial in a journal:

Giordano SP. What's that sound? (editorial) Respir Care 2000;45(10):1167-1168.

Editorial with no author given:

The perils of paediatric research (editorial). Lancet 1999;353(9154):685.

Letter in journal:

Piper SD. Testing conditions for nebulizers (letter). Respir Care 2000;45(8):971.

Book: (For any book, specific pages should be cited whenever reference is made to specific statements or other content.)

Cairo JM, Pilbeam SP. Mosby's respiratory care equipment, 6th ed. St Louis: Mosby; 1999:76-85.

Corporate author book:

American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

Chapter in book with editor(s):

Isono S. Upper airway muscle function during sleep. In: Loughlin GM, Carroll JL, Marcus CL, editors. Sleep and breathing in children: a developmental approach. (Lung Biology in Health and Disease, Vol 147, Claude Lenfant, Executive Editor.) New York/Basel: Marcel Dekker; 2000:261-291.

World Wide Web

American Lung Association. Trends in pneumonia, influenza, and acute respiratory conditions mortality and morbidity. February, 2000. http://www.lungusa.org/data. Accessed November 20, 2000.

Tables. Tables should be consecutively numbered. At the bottom of the table define and/or explain all abbreviations and symbols used in the table. For footnotes use the following symbols, superscripted, in the table body, in the following order: *, †, ‡, §, ‖, ¶, **, ††. If data include a "±" value, please indicate whether the value is a standard deviation or standard error of the mean.

Figures (illustrations). Figures include graphs, line drawings, photographs, and radiographs. All figures should be sharp black-and-white images and be camera-ready. Glossy prints are preferred, but a good laser print will do. Use only illustrations that clarify and augment the text. Radiographs should clearly illustrate the point being made and should be submitted as black-and-white glossy photographs. If color is essential to the figure, consult the Editorial Office for more information. In reports of animal experiments, use schematic drawings, not photographs. A letter of consent must accompany any photograph of an identifiable person. Number figures consecutively as Figure 1, Figure 2, etc. All the figures must be mentioned in the text. Every figure must have a legend (a title and/or description explaining the figure). Figure legends should appear as separate paragraphs at the end of the manuscript (after the References section), in the same computer file as the manuscript (not in a separate file, as with the tables and figures).

Do not create scanned versions of figures borrowed from other publications; clear photocopies are preferable. To include figures previously published in other publications you must obtain permission from the original copyright holder. Figures must be of professional quality and a copy of the article from which the figure came should be available.

Drugs. Precisely identify all drugs and chemicals used, giving generic (nonproprietary) names, doses, and methods of administration. Brand or trade names may be given in parentheses after generic names.

Commercial Products. In the text, parenthetically identify commercial products only on first mention, giving the manufacturer's name and location. Example: "We performed spirometry (1085 System, Medical Graphics, Minneapolis, Minnesota)." Provide model

numbers if available, and manufacturer's suggested price if the study has cost implications.

Permissions: You must obtain written permission to use pictures of identifiable individuals or to name individuals in the Acknowledgments section. You must obtain written permission from the original copyright holder to use figures or tables from other publications. Copies of all applicable permissions must be on file at RESPIRATORY CARE before a manuscript goes to press. Copyright is most often held by the journal or book in which the figure or table originally appeared and applies to the creativity, style, and form in which the facts/data are presented to the reader; the facts themselves are not copyright-protectable. Therefore, permission is required to reproduce a table or figure directly, or with minor adaptations, from a journal or book, but permission is not required if data are extracted and presented in a new format. In that case, cite the source of the data as in the following example: "Adapted from Reference 23."

Ethics. When reporting experiments on human subjects, indicate that procedures were conducted in accordance with the ethical standards of the *World Medical Association Declaration of Helsinki* (see Respir Care 1997;42(6):635-636; also available at *http://www.wma.net/e/17-c_eparagraphnumbering.html*) or of the institution's committee on human experimentation. State that informed consent was obtained. Do not use patients' names, initials, or hospital numbers in text or illustrations. When reporting experiments on animals, indicate that the institution's policy, a national guideline, or a law on the care and use of laboratory animals was followed.

Statistics. Identify the statistical tests used in analyzing the data and give the prospectively determined level of significance in the Methods section. Report p values in the Results section. Cite only textbook and published article references to support choices of tests. Parenthetically identify any computer programs used. If data include a "±" value, please indicate whether the value is a standard deviation or standard error of the mean.

Units of Measurement. Express all measurements in SI (*Système Internationale*) units (units and conversion factors listed at Respir Care 1997;42(6):640 and also available at *http://www.rcjournal.com/author_guide/*. Show gas pressures (including blood gas tensions) in millimeters of mercury (mm Hg).

Conflict of Interest. On the cover page, authors must disclose any liaison or financial arrangement they have with a manufacturer or distributor whose product is addressed in the manuscript or with the manufacturer or distributor of a competing product. Such arrangements do not disqualify a paper from consideration and are not disclosed to reviewers. Reviewers are screened for possible conflict of interest.

Abbreviations and Symbols. Use the standard abbreviations and symbols listed at Respir Care 1997;42(6):637-642 (also available at *http://www.rcjournal.com/author_guide/*). Do not create new abbreviations. Do not use abbreviations in the title or section headings and do not use unusual abbreviations in the abstract. Use an abbreviation only if the term occurs 4 or more times in the paper. Parenthetically define *all* abbreviations: write out the full term on first mention, followed by the abbreviation in parentheses. Example: chronic obstructive pulmonary disease (COPD). Thereafter use only the abbreviation. Standard units of measurement and scientific terms can be abbreviated without explanation (eg, L/min, mm Hg, pH, O_2).

Please use the following forms: cm H_2O (not cmH2O), f (not bpm), L (not l), L/min (not LPM, l/min, or lpm), mL (not ml), mm Hg (not mmHg), pH (not Ph or PH), $p > 0.001$ (not $p>0.001$), s (not sec), S_{pO2} (arterial oxygen saturation measured via pulse-oximetry).

Prior and Duplicate Publication. In general, do not submit work that has been published or accepted elsewhere, though in special instances the Editor may consider such material if the original publisher grants permission. Please consult the Editor before submitting such work.

Authorship. All persons listed as authors must have participated in the reported work and in the shaping of the manuscript, all must have proofread the submitted manuscript, and all should be able to publicly discuss and defend the paper's content. A paper of corporate authorship must specify the key persons responsible for the article. Attribution of authorship is not based solely on solicitation of funding, collection or analysis of data, provision of advice, or similar services. Persons who provide such ancillary services may be recognized in an Acknowledgments section, but written permission is required from the persons acknowledged.

Reviewers: Please supply the names, credentials, affiliations, addresses, and phone/fax numbers of 3 professionals whom you consider expert on the topic of your paper. Your manuscript may be sent to one or more of them for blind peer review.

Submitting the Manuscript

Submit 3 printed copies and one (3.5-inch) computer diskette. The printed copies should each include photocopies of all of the Figures, Tables, and Appendixes. On the diskette, the manuscript should be in one file and the tables in a separate file. If soft copies of the figures are available, they should also be in a separate file. *However, do not create scanned versions of figures borrowed from other publications; clear photocopies are preferable.* Include the completed Cover Letter and Checklist (see next page) and permission letters. Mail to RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104. Do not fax manuscripts. Receipt will be acknowledged.

RESPIRATORY CARE
Editorial Office:

600 Ninth Avenue, Suite 702
Seattle WA 98104

(206) 223-0558 (voice)
(206) 223-0563 (fax)
rcjournal@aarc.org

Cover Letter & Checklist

A copy of this completed form must accompany all manuscripts submitted for publication.

Title of Paper: _____

Publication Category: _____

Corresponding Author: _____ Phone: _____ FAX: _____

Mailing Address: _____

Reprints: ❑ Yes ❑ No E-mail Address: _____

"We, the undersigned, have all participated in the work reported, proofread the accompanying manuscript, and approve its submission for publication." Please print and include credentials, title, institution, academic appointments, city and state. If more than 4 authors, please use another copy of this form.*

*First Author: _____

Author Signature/Date _____

*Second Author: _____

Author Signature/Date _____

*Third Author: _____

Author Signature/Date _____

*Fourth Author: _____

Author Signature/Date _____

Has this research been presented in any public forum? ❑ Yes ❑ No

If yes, where, when and by whom? _____

Has this research received any awards? ❑ Yes ❑ No

If yes, please describe. _____

Has this research received any grants or other support, financial or material? ❑ Yes ❑ No

If yes, please describe. _____

Do any of the authors of this manuscript have a financial interest in (or a commercial or consulting relationship to) any of the products or manufacturers mentioned in this paper or any competing products or manufacturers? ❑ Yes ❑ No

If yes, please describe. _____

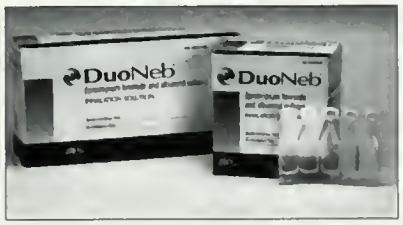
CHECKLIST

- ❑ Have you enclosed a copy of the manuscript on diskette?
- ❑ Is double-spacing used throughout entire manuscript?
- ❑ Are all pages numbered in upper-right corners?
- ❑ Are all references, figures, and tables cited in the text?
- ❑ Has the accuracy of the references been checked, and are they correctly formatted?
- ❑ Have SI values been provided?
- ❑ Has all arithmetic been checked?
- ❑ Have generic names of drugs been provided?
- ❑ Have necessary written permissions been provided?
- ❑ Have authors' names been omitted from text and figure labels?
- ❑ Have copies of 'in press' references been provided?
- ❑ Has the manuscript been proofread by all the authors?
- ❑ Have the manufacturers and their locations been provided for all devices and equipment used?

News releases about new products and services will be considered for publication in this section. There is no charge for these listings. Send descriptive release and glossy black and white photographs to RESPIRATORY CARE, New Products & Services Dept, 11030 Ables Lane, Dallas TX 75229-4593. The Reader Service Card can be found at the back of the Journal.

New Products & Services

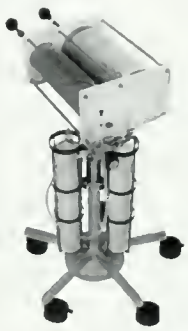
Miniature Orifice. The Lee Company calls its new IMH orifice for liquids an economical, highly accurate miniature restrictor that can be used in medical instrumentation and disposables, hydraulic controls, and commercial and industrial applications. According to the company, the device is now available in 53 standard flow rates and the stainless steel orifice is 100% flow tested in both directions to ensure flow tolerance as tight as ± 2%. Lee Company press materials say the new device utilizes the company's field-proven controlled expansion principle that makes it easy and economical to install, provides retention up to 21 Mpa (3,000 psi) and crates a leak-tight seal that prevents any by-pass leakage. For more information from The Lee Company, circle number 169 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/



Dual-Therapy Nebulizer Solution. Dey LP, an Associate of Merck KGaA in Germany, has announced the FDA approval of DuoNeb (ipratropium bromide and albuterol sulfate) inhalation solution for the treatment of bronchospasm associated with COPD in patients who require more than one bronchodilator. According to Dey, DuoNeb combines two well-known respiratory solutions, albuterol sulfate and ipratropium bromide, in one premixed premeasured, unit-dose vial for nebulization. Dey press materials say the premixed and premeasured solution offers several advantages: faster treatment time, reduced chance for medication error, lower risk of cros-contamination, and less waste. For more information from Dey LP, circle number 170 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Oxygen Monitor. Radiometer America Inc launches their multi-channel transcutaneous oxygen monitor — the TCM400. Company press materials describe the new device as fully portable, modular system which an simultaneously monitor up to six different sites on a patient. According to Radiometer, the results produced by the TCM400 are reliable and reproducible as the instrument houses an internal barometer that automatically calculates the correct calibration value. The company says pressing one button calibratres all 6 electrodes within 2-3 minutes. For more information from Radiometer America, circle number 171 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Anti-Stick Surgical Glove. Trademark Medical introduces their physician-invented, puncture-proof, surgical gimbel gloves. According to Trademark, their new gloves provide a 1000% increase in protection over double gloving with latex. The company says the fingertip pads provide significant protection against punctures from needles, wires, bone fragments, and cuts/slashes from scalpels and other sharp objects. Press materials also explain that the gloves minimize the potential threat of latex allergy by exceeding the new proposed FDA requirements for water-soluable misero-thin polymer mesh protein levels. For more information from Trademark Medical, circle number 172 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/



DLco Simulator. Hans Rudolph Inc introduces the new DLco Simulator with Easy Lab QC Software for use with single-breath carbon monoxide diffusing capacity (DLco) equipment. According to the manufacturer, the 5560 Series Simulator allows for checking the accuracy and variability of a DLco instrument. Hans Rudolph claims that the Easy Lab QC Software aids in defining how the instrument computes DLco, charting and graphing the instrument's performance against the Simulator's projected values. It also charts and graphs the comparison of the data obtained from biological control subjects and performs linearity checks of gas analyzers. When configured with the appropriate precision gases for various DLco devices, according to the manufacturer, it will accurately produce a wide range of DL values. For more information from Hans Rudolph, circle number 173 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Calendar of Events

Date	AARC & State Society Programs	Contact
Aug. 14	Professor's Rounds 2001 Live Videoconference, Program 6	AARC, (972) 243-2272
Aug. 29–31	West Virginia Society for Respiratory Care's Respiratory Reunion; **Charleston, WV**	Jay Wildt at (304) 442-7474 or jay.wildt@mghwv.org; or Anna Parkman at (304) 357-4837 or AParkman@ucwv.edu
Sept. 11	Professor's Rounds 2001 Teleconference, Program 6	AARC, (972) 243-2272
Sept. 10-12	Hawaii Society for Respiratory Care's 28th Annual State Respiratory Conference; **Waikiki Beach, HI**	Trace Ono at (808) 547-4241 or tracemaz@compuserve.com; www.rcphawaii.org
Sept. 12–14	MD/DC Society for Respiratory Care, 20th Annual Conference by the Sea, **Ocean City, MD**	Joe Lynott at (202) 877-6086 or joseph.p.lynott@medstar.net; or Tom Striplin at (301) 784-5523 or tstriplin@mindspring.com
Sept. 12–14	Alabama Society for Respiratory Care's Annual Meeting, **Birmingham, AL**	Bill Pruitt, (334) 434-3405, wpruitt@jaguar1.usouthal.edu
Sept. 25	Professor's Rounds 2001 Live Videoconference, Program 7	AARC, (972) 243-2272
Sept. 26–27	MSRC Annual Meeting, **Sturbridge, MA**	Valeri-Ann Bolduc, (508) 429-7478, O2val@aol.com
Oct. 16	Professor's Rounds 2001 Teleconference, Program 7	AARC, (972) 243-2272
Oct. 25-26	New Jersey Society for Respiratory Care's 2001 Shore Conference; **Atlantic City, NJ** www.njsrc.org	Maura McGovern at (973) 537-3919 or mmcgovern@saintclares.org;
Dec. 1–4	47th International Respiratory Congress; **San Antonio, TX**	AARC, (972) 243-2272, www.aarc.org
Feb. 6–8, 2002	West Virginia Society for Respiratory Care's Winter Meeting, **Davis, WV**	Jay Wildt at (304) 442-7474 or jay.wildt@mghwv.org; or Anna Parkman at (304) 357-4837 or AParkman@ucwv.edu

Date	Other Meetings	Contact
Oct. 9–11	Cardiorespiratory Diagnostics 2001; **Las Vegas, NV**	Medical Graphics Corporation, Mari Orke, (800) 950-5597, ext. 444, www.medgraph.com
Oct. 29	University of Cincinnati Medical Center's Pulmonary Function Training Course; **Cincinnati, OH**	Dr. Roy McKay at (513) 558-1234 or info@DrMcKay.com; www.DrMcKay.com
March 20–23, 2002	21st Annual Big Sky Pulmonary & Critical Care Medicine Conference; **Big Sky, MT**	American Lung Association of the Northern Rockies, (406) 442-6556, ala-nr@ala-nr.org

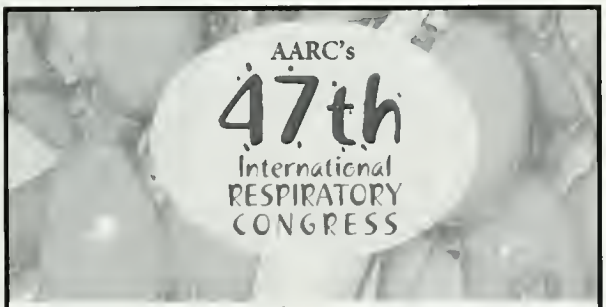
Notices of competitions, scholarships, fellowships, examination dates, new educational programs and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593

Scheduled Professor's Rounds 2001

Program #6 New Respiratory Drugs: What, When, and How—Joseph L Rau PhD RRT FAARC; Host Patrick J Dunne MEd RRT FAARC—Video August 14 Audio September 11

Program #7 Invasive Ventilation: The Latest Word—Richard H Kallet MS RRT; Host Richard D Branson BA RRT FAARC—Video September 25 Audio October 16

Program #8 Test Your Lungs-Know Your Numbers-Prevent Emphysema—Thomas L Petty MD FAARC; Host David J Pierson MD FAARC—Video October 23 Audio November 20



December 1-4, 2001
San Antonio, Texas

Don't Confuse the AARC International Congress with Other Meetings —
This is the Only Official Congress of the AARC.

Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org
- Current job listings
- American Respiratory Care Foundation fellowships, grants, & awards
- Clinical Practice Guidelines

National Board for Respiratory Care
http://www.nbrc.org

RESPIRATORY CARE online
http://www.rcjournal.com
- Subject and Author Indexes
- Contact the editorial staff
- OPEN FORUM; submit your abstract online

Asthma Management Model System
http://www.nhlbi.nih.gov

Keys to Professional Excellence
http://www.aarc.org/keys/

Committee on Accreditation for Respiratory Care
http://www.coarc.com

The National Board for Respiratory Care—Examination Fees for 2001

Examination	Examination Fees
CRT	$190 (new applicant) $150 (reapplicant)
Perinatal/Pediatric	$250 (new applicant) $220 (reapplicant)
CPFT	$200 (new applicant) $170 (reapplicant)
RPFT	$250 (new applicant) $220 (reapplicant)
RRT (Written & CSE)	$190 (new) $150 (reapplicant) written only $200 (new and reapplicant) CSE only $390 (new) $350 (reapplicant) both

For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156, or e-mail: nbrc-info@nbrc.org

Authors in This Issue

Ambrosino, Nicolino 834
Ayers, Leona W 783
Barrington, Keith J 829
Beckett, Ronald G 833
Blanch, Paul B 789
Buist, A Sonia 798
Bunnell, J Bert 826
Calverley, Peter MA 798
Cordero, Leandro 783
Durning, Suzanne M 772
Ferranti, Redento D 830
Francis, Barbara 772
Godinez, Rodolfo I 772
Hales, Roberta 772
Hess, Dean R 826
Hurd, Suzanne S 798
Jenkins, Christine R 798
Lin, Richard H 772
Napoli, Linda 772
Pauwels, Romain A 798
Pierson, David J 768
Sananes, Mercedes 783
Schultz, Theresa Ryan 772
Theodoropoulos, Demetrios S 832
Tyler, Lisa 772
Votto, John J 830
Watzman, H Marc 772
Woodson, Arnetta 772

Advertisers in This Issue

To advertise in RESPIRATORY CARE, contact Tim Goldsbury, 380 Tequesta Drive, Tequesta FL 33469 at (561) 745-6793, Fax (561) 745-6795, e-mail: goldsbury@aarc.org, for rates and media kits. For recruitment/ classified advertising contact Beth Binkley, Marketing Assistant for RESPIRATORY CARE, at (972) 243-2272, Fax (972) 484-6010. Dale Griffiths is the Marketing Director for RESPIRATORY CARE.

Company	Product	Circle #	Phone	Page #
Clear Medical	Reuseable Medical Devices	123	800-426-1042	755
DEY	DuoNeb Inhalation Solution	150	800-755-5560	C2, 737, 738
DHD Healthcare	EZ-PAP	137	800-847-8000	C4
Futuremed	Spirometry Systems	128	800-222-6780	754
GlaxoSmithKline	Serevent	124	SEE AD	746-749
Hans Rudolph Inc	Research Pneumotach Systems	127	800-456-6695	753
Jones Medical	Satellite Spirometer	140	800-323-7336	761
Kaiser Permanente	Recruitment	121	800-331-3976	753
Monaghan	AeroChamber Plus	125	800-833-9653	744
ndd Technologies	EasyOne Spirometry Systems	126	377-904-0090	C3
Praxair Inc	Portable Oxygen Unit	122	800-299-7977	742
Siemens	Corporate Ad	131	SEE AD	763
Siemens	Corporate Ad	132	SEE AD	765
Siemens	Corporate Ad	133	SEE AD	767
Tyco Puritan Bennett	840 Ventilator	145	800-635-5267	740

COPYRIGHT INFORMATION. RESPIRATORY CARE is copyrighted by Daedalus Enterprises Inc. Reproduction in whole or in part without the express written permission of Daedalus Enterprises Inc is prohibited. Permission to photocopy a single article in this Journal for noncommercial purposes of scientific or educational advancement is granted. Permission for multiple photocopies and copies for commercial purposes must be requested in writing, via e-mail (rejournal@aarc.org), or telephone and approved by RESPIRATORY CARE. Anyone may, without permission, quote up to 500 words of material in this journal provided the quotation is for noncommercial use and RESPIRATORY CARE is credited. Longer quotation requires written approval by the author and publisher. Single reprints are available only from the authors. Reprints for commercial use may be purchased from Daedalus Enterprises Inc. For more information and prices call (972) 243-2272.

DISCLAIMER. The opinions expressed in any article or editorial are those of the author and do not necessarily reflect the views of the Editors, the American Association for Respiratory Care (AARC), or Daedalus Enterprises Inc. Neither are the Editors, the AARC, or the Publisher responsible for the consequences of the clinical applications or use of any methods or devices described in any article or advertisement.

SUBSCRIPTION RATES. Individual subscription rates are $75 per year (12 issues), $145 for 2 years, and $215 for 3 years in the US and Puerto Rico. Rates are $90 per year, $175 for 2 years, and $260 for 3 years in all other countries (add $94 per year for air mail). Single copies when available cost $10; add $9 for air mail postage to overseas countries. Checks should be made payable to RESPIRATORY CARE and sent to the subscription office at 11030 Ables Lane, Dallas TX 75229-4593, or call (972) 243-2272.

SUBSCRIPTION RATES FOR ASSOCIATIONS. Basic annual subscriptions are offered to members of associations according to their membership enrollment: 101-500 members = $16.25/year (each); 501-1,500 = $15.75/year (each); 1,500-10,000 = $14.75/year (each); more than 10,000 = $13.75/year (each). For information, contact Ray Masferrer at (972) 243-2272.

CHANGE OF ADDRESS. Notify the AARC at (972) 243-2272 as soon as possible of any change in address. Note the subscription number (from the mailing label) and your name, old address, and new address. Allow 6 weeks for the change. To avoid charges for replacement copies of missed issues, requests must be made within 60 days in the US and 90 days in other countries.

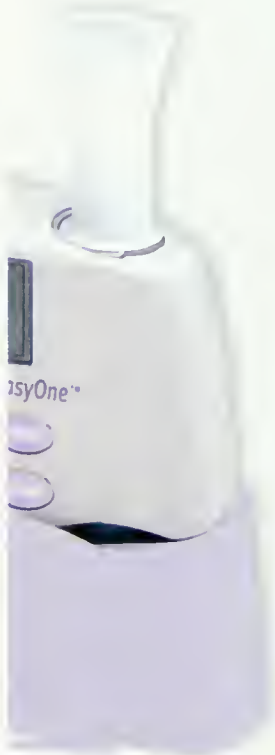
MANUSCRIPTS. The Journal publishes clinical studies, method/device evaluations, reviews, and other materials related to cardiopulmonary medicine and research. Manuscripts may be submitted to the Editorial Office, RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104. Instructions for authors are printed in every issue.

Ultrasonic Spirometry... A Breakthrough in Pulmonary Function Testing

ndd Medical Technologies introduces the *EasyOne*™ Spirometry Technology.

re are no codes to
) moving parts to
hpiece eliminates
.

s a portable, full-
ures you expect,
tions



Proud sponsor of

National Lung Health Education Program

8) 244-0619

Subscription

RESPIRATORY CARE
Subscription Form

RESPIRATORY CARE is the most highly regarded peer-reviewed scientific publication for the Clinician participating in the evaluation and care of patients with cardiopulmonary problems. Please print; incomplete forms will not be processed. For faster service, fax to (972)484-2720

DON'T MISS A SINGLE ISSUE!

	U.S. Subscriptions	Subscriptions Outside U.S.
1 YR (12 issues)	☐ $75	☐ $90
2 YRS (24 issues)	☐ $145	☐ $175
3 YRS (36 issues)	☐ $215	☐ $260

Enclosed is a check in the amount of $ _____

Charge to my:
- ☐ Mastercard
- ☐ Visa
- ☐ Bill Me

Signature _____ Expiration Date _____ Credit Card Number _____

Name _____ Title _____

Facility Name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____

RESPIRATORY CARE

FREE

Product Information

Receive FREE information on the products and services mentioned in this issue, by circling the corresponding advertiser's number. Fill in your name and address and mail this postage-paid card. Information will be sent directly to you from the manufacturer. Incomplete forms will not be processed.

MAIL TODAY OR FOR FASTER SERVICE FAX TO (609) 786-4415

For AARC membership information, circle 101 For Respiratory Care subscription information, circle 102

101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118
119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136
137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154
155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172
173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190
191 192 193 194 195 196 197 198 199 200

Please circle no more than 15 items.

Name _____ Title _____

Facility Name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____

August 2001 Expires 11/15/01

RESPIRATORY CARE

I TYPE OF INSTITUTION OR PRACTICE
1 ☐ Hospital
2 ☐ Skilled Nursing Facility
3 ☐ Subacute Care Facility
4 ☐ Home Care Practice
5 ☐ School
6 ☐ Distributor

II DEPARTMENT
A ☐ Respiratory Care
B ☐ Cardiopulmonary
C ☐ Subacute Care
D ☐ Home Care

III SPECIALTY
1 ☐ Clinician
2 ☐ Perinatal/ Pediatrics
3 ☐ Critical Care
4 ☐ Research
5 ☐ Subacute Care
6 ☐ Diagnostics/ Pulmonary Function
7 ☐ Management
8 ☐ Home Care
9 ☐ Rehabilitation
10 ☐ Education

IV POSITION
A ☐ Department Head
B ☐ Chief Therapist
C ☐ Supervisor
D ☐ Staff Therapist/ Technician
E ☐ Medical Director
F ☐ Educator/Instructor
G ☐ Sales
H ☐ Other (please specify)

V ARE YOU AN AARC MEMBER?
1 ☐ Yes 2 ☐ No

Authors in This Issue

Ambrosino, Nicolino 834
Ayers, Leona W 783
Barrington, Keith J 829
Beckett, Ronald G 833
Blanch, Paul B 789
Buist, A Sonia 798
Bunnell, J Bert 826
Calverley, Peter MA 798
Cordero, Leandro 783
Durning, Suzanne M .
Ferranti, Redento D ..
Francis, Barbara ....
Godinez, Rodolfo I ..
Hales, Roberta .....
Hess, Dean R 826
Hurd, Suzanne S 798
Jenkins, Christine R 798
Lin, Richard H 772
Napoli, Linda 772
Pauwels, Romain A 798
Pierson, David J 768
Sananes, Mercedes 783
Schultz, Theresa Ryan 772

Advertis in This Iss

Company
Clear Medical
DEY
DHD Healthcare
Futuremed
GlaxoSmithKline
Hans Rudolph Inc
Jones Medical
Kaiser Permanente
Monaghan
ndd Technologies
Praxair Inc
Siemens
Siemens
Siemens
Tyco Puritan Bennett

COPYRIGHT INFORMA
Daedalus Enterprises Inc. R
written permission of Daed
photocopy a single article
scientific or educational a
photocopies and copies for
ing, via e-mail (rcjournal@
RATORY CARE. Anyone m
material in this journal prov
RESPIRATORY CARE is
proval by the author and pul
authors. Reprints for comm
terprises Inc. For more info

DISCLAIMER. The opinio
of the author and do not
American Association for
prises Inc. Neither are the
for the consequences of the
vices described in any artic

SUBSCRIPTION RATES.
(12 issues), $145 for 2 ye
Rico. Rates are $90 per year

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 2480 Dallas,TX
POSTAGE WILL BE PAID BY ADDRESSEE

AARC Subscriptions
ATTN: Beth Binkley
PO BOX 29686
Dallas TX 75229-9691

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 881 Riverton, NJ
POSTAGE WILL BE PAID BY ADDRESSEE

AARC Publications
PO BOX 11605
Riverton NJ 08076-7205

Ultrasonic Spirometry... A Breakthrough in Pulmonary Function Testing

ndd Medical Technologies introduces the *EasyOne*™ Spirometry System, the first to use Ultrasonic Flow Measurement Technology.

Ultrasonic delivers!

The open flow path eliminates hassles. There are no codes to enter, no screens to catch sputum, and no moving parts to gum-up or wear out. The hygienic mouthpiece eliminates the need for cleaning between patients.

The *EasyOne*™ Diagnostic Spirometer is a portable, full-function unit packed with all the features you expect, and meets the 1994 ATS recommendations for diagnostic spirometry.

Also available is the *EasyOne*™ Frontline Spirometer, a simpler version designed for quick assessment.

NEW! The *EasyWare*™ software allows you to interface the *EasyOne*™ spirometer with a pc.

Contact us to find out how Ultrasonic Flow Measurement can make spirometry faster, easier, more reliable, and more affordable for you.

ndd Medical Technologies, Inc.
www.nddmed.com

Proud sponsor of
National Lung Health Education Program

Phone (877) 904-0090 ■ **Fax:** (978) 244-0619

Circle 126 on product info card

Need more aggressive lung expansion therapy? Now, your choice is EZ.

New EZ-PAP.™ The EASY option for atelectasis.

When incentive spirometry alone won't open patients' airways, expand your options with new EZ-PAP. It makes providing positive airway pressure positively easy. Simply connect to a flow meter (wall air or O_2 for enhanced FiO_2), adjust to 5-15 lpm, and instruct the patient to breathe diaphragmatically through the mouthpiece or mask. No equipment to roll around. No labor-intensive CPT. No extensive training. Just a few minutes of therapy, once an hour — not for hours at a time.

EZ-PAP features a pressure port for connection to a gauge (recommended for initial use with each patient), and standard 22-mm OD fitting to accommodate a mouthpiece or 3 mask options. For more information, call DHD Healthcare toll-free today: **1-800-847-8000.**

DHD Healthcare

Innovations for respiratory care

One Madison Street, Wampsville, NY 13163 USA
(800) 847-8000 (315) 363-2330 FAX (315) 363-5694
www.dhd.com

EZ-PAP is a trademark of DHD Healthcare Corporation
© 1997 DHD Healthcare Corporation

Circle 137 on product info card